Handheld PDA Review

UTMJ

University of Toronto Medical Journal
Volume 78, Number 3/May, 2001
A student-run scientific publication. Established in 1923.

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Preface from the Editors

The final 2000-2001 issue of the *UTMJ* showcases a wide variety of articles that are sure to provide topics of interest for everyone. It begins with an overview of the Human Genome Project that separates fact from fiction in discussing the impact of the project's results on biomedical research. Friedman *et al.* review acromegaly, from its molecular pathophysiology to its clinical presentation and recent advances in treatment. The review's scope will engage everyone from the undifferentiated reader to the experienced endocrinologist. Kerba then provides us with an in-depth analysis of health-related quality of life and utility theory. The final review article by Kundhal *et al.*, probes the issues surrounding Crohn's disease in the pediatric population, and reports on the numerous etiological factors implicated in this form of inflammatory bowel disease. From human genetics to internal medicine to community health, these feature articles are sure to appeal to a broad range of medical trainees and professionals.

In our Prolific Clinician Profile, we interview esteemed Professor of Surgery, Tirone David. As a world-class cardiac surgeon, Dr. David has gained international acclaim for his clinical research. The Law and Ethics section features a timely discussion on the issue of medical students' ability to speak out about their supervisors' improprieties. In this piece, Misir discusses the intricacies of coping with unethical behaviour as a medical trainee. The Forum probes the issue of physician report cards, with perspectives from both medical students and physicians. Our News and Views section concludes with back-to-back Back to Basics articles. The first is the conclusion of a two-part series on acid-base disturbances, this time reviewing alkalemias and mixed disturbances. The second primer explores the management of burn injuries, and provides an excellent approach for treating minor burns.

In this issue, the Clinicopathological Correlation examines an unwanted traveling companion, as it delves into the differential diagnosis of a fixed, painful cutaneous nodule. Quick Diagnosis takes a pediatric turn with case reports taken from the Hospital for Sick Children; fascinating dermatological, rheumatological and infectious disease cases are also presented. The Morning Report takes the reader to the bedside, reviewing a classic case of an unusual metabolic disease. For the technophiles among us, hardware and software aspects of handheld personal digital assistants ("PDAs") are explored, with a thorough review of the technology to date. Rounding off this final issue is an examination of the realities and misconceptions surrounding Canada's postulated brain drain, followed by a series of book reviews, ranging from pathophysiology to fiction – books that would be welcome additions to any collection.

With this last issue of the 78th volume, our tenure as editors comes to an end. We would like to take this opportunity to acknowledge those who have played a part in the continuing success of the *UTMJ*. Our staff, writers and editors alike, truly form the heart and soul of the journal, and without their contributions this venture would have been impossible. Their commitment to the *UTMJ* over this past year has been instrumental to the journal's success, and we commend their efforts. As well, we would like to acknowledge our faculty advisory board for their support, especially the chair of the board, Dr. Allan Detsky, who has provided invaluable support for the *UTMJ* since his mandate began. This issue features a newly-created Awards page to acknowledge those individuals who have gone above and beyond the call of duty to enhance the quality of the journal. Lastly, we would like to thank our subscribers who, with their continued contributions, have allowed Canada's oldest student-run medical journal to thrive and blossom into a highly regarded publication for all health professionals and students to enjoy.

As we hand off the editorial torch, we look forward to the promising future of the *UTMJ*. With its newly revamped website (www.utmj.org) and its growing subscriber base, its ascent has only begun. We feel confident that the journal will continue to grow in its role as a medium for student publishing and medical education.

Prateek Lala
Valerie Panet-Raymond
Editors-in-Chief

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ACTIONS AND CLINICAL PHARMACOLOGY

[illegible] synthetic lipid lowering agent. It is a selective, competitive inhibitor of 3 hydroxy 3 [illegible] HMG-CoA reductase. This enzyme catalyzes the conversion of HMG CoA to mevalonate, [illegible] rate-limiting step in the biosynthesis of cholesterol.

[illegible] cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in [illegible] and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell surface for [illegible] uptake and catabolism of Low Density Lipoprotein (LDL).

[illegible] LDL cholesterol (LDL-C) and the number of LDL particles. LIPITOR also reduces Very Low Density [illegible] cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the [illegible] of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated [illegible] cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Elevated [illegible] TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with [illegible] decreased HDL-C or increased LDL-C.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. After tablet administration, [illegible] 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 litres. Atorvastatin is >98% bound to plasma proteins. Atorvastatin is [illegible] extensively metabolized by cytochrome P-450 3A4 to ortho- and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG Co-A reductase is attributed to active [illegible] metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered [illegible] following oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol, (total C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa),
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern,
- Dysbetalipoproteinemia (Type III),
- Hypertriglyceridemia (Type IV)
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25 - 56%) and LDL-C levels (23 - 40%). Chylomicrons, which characterize Types I and V, have not been measured in clinical studies in patients with high TG levels (> 11 mmol/L).

In an open label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open label study in patients with homozygous familial hypercholesterolemia (FH), LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG < 4.52 mmol/L (< 400 mg/dL), LDL-C can be estimated using the following equation:

$$\text{LDL-C (mmol/L)} = \text{total-C} - [(0.37 \times \text{TG}) + \text{HDL-C}]$$

$$\text{LDL-C (mg/dL)} = \text{total-C} - [(0.2 \times \text{TG}) + \text{HDL-C}]$$

For patients with TG levels > 4.52 mmol/L (> 400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

The Atorvastatin Versus Revascularization Treatments (AVERT) study examined the effect of intensivre lipid-lowering in patients with stable coronary artery disease and LDL-C at least 3.0 mmol/L in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Patients were randomised for 18 months to LIPITOR 80 mg daily or to PTCA with usual medical care which could include lipid metabolism regulators. The results of the AVERT study should be considered as exploratory since several limitations may affect its design and conduct. In the medical-treated group with LIPITOR there was a trend for a reduced incidence of ischemic events and time to first ischemic event. The results also suggest that intensive treatment to target LDL-C levels with LIPITOR is **additive and complementary** to angioplasty and would benefit patients referred for this procedure (see SELECTED BIBLIOGRAPHY).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

[illegible] liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of [illegible] (see WARNINGS).

[illegible] and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

[illegible] HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which [illegible] be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. [illegible] metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this [illegible] (see WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated [illegible]).

Hepatic Effects

[illegible] increases in serum transaminases greater than three times the upper limit of normal occurred [illegible] received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was [illegible], serum transaminase levels returned to pretreatment levels. The increases were [illegible] not jaundice or other clinical signs or symptoms. Most patients continued treatment with a [illegible] sequelae.

[illegible] be performed before the initiation of treatment, and periodically thereafter. Special attention [illegible] patients developing elevated serum transaminase levels, and in these patients measurements should [illegible] performed more frequently.

If [illegible] in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of [illegible], particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the [illegible] should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR, if such a condition should develop during therapy, the drug should be discontinued.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic studies conducted in healthy subjects with erythromycin and clarithromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions). Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors. LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity or mortality or total mortality have not been established.

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) levels. Until further experience is obtained, it is suggested, where feasible, that measurements of serum Lp(a) be followed up in patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics, SELECTED BIBLIOGRAPHY).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions).

Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Pharmacokinetic Interaction Studies and Potential Drug Interactions

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also Geriatric Use; Renal Insufficiency; Patients with Severe Hypercholesterolemia).

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least two hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is no experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration (see WARNINGS, Muscle Effects).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).

Digoxin: In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily (see Human Pharmacokinetics). Patients taking digoxin should be monitored appropriately.

Antihypertensive agents (amlodipine): In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state (see Human Pharmacokinetics).

Oral Contraceptives and Hormone Replacement Therapy: Coadministration of LIPITOR with an oral contraceptive, containing 1 mg norethindrone and 35µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox™ TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4 Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e. erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), or the antidepressant, nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; SELECTED BIBLIOGRAPHY).

In healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. pre-existing prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin): In healthy adults, coadministration of LIPITOR (10 mg OD) and azithromycin (500 mg OD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg OD) with erythromycin (500 mg QID) or clarithromycin (500 mg BID), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin approximately 40% and 80%, respectively (see WARNINGS, Muscle Effects; Human Pharmacokinetics).

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions; DOSAGE AND ADMINISTRATION).**

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and CPK levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid-lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

TABLE 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials

	Placebo % (n=270)	LIPITOR % (n=1122)
GASTRDINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVDUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports: severe myopathy with or without rhabdomyolysis (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated reports: thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis). These may have no causal relationship to atorvastatin.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the American Heart Association (AHA) Step 1 diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented. Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia, Including Familial Combined Hyperlipidemia: The recommended dose of LIPITOR is 10 mg once a day. The majority of patients achieve and maintain target cholesterol levels with LIPITOR 10 mg/day. A significant therapeutic response is evident within two weeks, and the maximum response is usually achieved within two to four weeks. The response is maintained during chronic therapy.

Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. Doses should be individualized according to baseline LDL-C and/or TG levels, the desired LDL-C and/or TG target (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Dyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP]), the goal of therapy and the patient's response. Adjustments of dosage, if necessary, should be made at intervals of four weeks or more. The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients (see section below).

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

The following reductions in total cholesterol and LDL-C levels have been observed in two dose-response studies and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia.

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia (Mean Percent Change from Baseline)[a]

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L[b] (273 mg/dL)[b]	-29	-33	-37	-45
LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b]	-39	-43	-50	-60

[a]Results are pooled from 2 dose-response studies.
[b]Mean baseline values.

Severe Dyslipidemias:

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions).

Concomitant Therapy

See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency

See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance

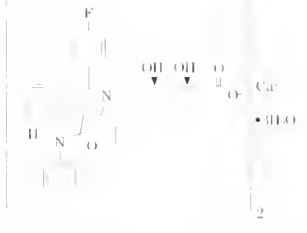
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$

Molecular Weight: 1209.42

Structural Formula:



Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition:

Each tablet contains either 10 mg, 20 mg or 40 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations:

Store at controlled room temperature 15 to 25°C.

AVAILABILITY OF DOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg and 40 mg atorvastatin per tablet.

10 mg: White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

20 mg: White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other. Available in bottles of 90 tablets.

40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PD 157" on the other. Available in bottles of 90 tablets.

References:

1. Smith *et al.* Cost of Treating to a Modified European Atherosclerosis Society LDL-C Target — Comparison of Atorvastatin with Fluvastatin, Pravastatin and Simvastatin. *Clin Drug Invest* 1999 Mar;17(3):185-193. 2. LIPITOR (atorvastatin calcium) Product Monograph, Pfizer Canada Inc., June 2000. 3. Bertolini S, Bitolfo Bon G, Campbell LM, Farnier M, Langan J, Mahla G, Pauciullo P, Sirtori C, Egros F, Fayyad R, Nawrocki J. The efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis* 1997;130:191-197. 4. Dart A, Jerums G, Nicholson G, d'Emden M, Hamilton-Craig I, Tallis G, Best J, West M, Sullivan D, Bracs P, Black D. A multicenter, double-blind, 1-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol* 1997;80:39-44. 5. Ontario Drug Benefit Formulary, April 1999

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The Human Genome Project

Nicholas Tan, B.Sc (0T3)

Abstract

Throughout this past year, the Human Genome Project has attracted considerable public attention. Movie scriptwriters, science fiction authors and the popular press alike have all elaborated, inaccurately more often than not, the significance of the Human Genome Project. This article seeks to present the facts concerning the history and results of the Human Genome Project, as well as to discuss its immediate impact on biomedical research.

Introduction

The Human Genome Project (HGP) was first conceived in the mid-1980s by two prominent scientists, Robert Sinsheimer and Nobel laureate Renatto Dulbecco, to help in the fight against cancer. In 1990, the HGP kicked off as a public joint international consortium including the United States of America, Asia, and Europe, with funding coming from both government agencies and public charities (see Box 1).[1]

Box 1

Member institutions of the Human Genome Sequencing Consortium

Baylor College of Medicine, Houston, Texas, USA

Beijing Human Genome Center, Institute of Genetics, Chinese Academy of Sciences, Beijing, China

Department of Molecular Biology, Keio University, Tokyo, Japan

Gesellschaft fur Biotechnologische Forschung GmbH, Braunschweig, Germany

Genome Analysis Group, International.

Genome Therapeutics Corporation, Waltham, MA, USA

Genoscope, Evry, France

Human Genome Center, Stanford, Palo Alto, CA, USA

Institute of Molecular Biotechnology, Department of Genome Analysis, Jena, Germany

Joint Genome Institute, U.S. Department of Energy, Walnut Creek, CA, USA

Lita Annenberg Hazen Genome Center, Cold Spring Harbor Laboratory, New York, USA

Max Planck Institute for Molecular Genetics, Berlin, Germany

National Human Genome Research Institute, NIH, MD, USA

RIKEN Genomic Sciences Center, Saitama, Japan

Stanford Genome Technology Center, Palo Alto, CA, USA

The Sanger Centre, Hinxton, U.K.

University of Oklahoma's Advanced Center for Genome Technology, OK, USA

The Institute for Systems Biology: Multimegabase Sequencing Center, Seattle, WA, USA

University of Texas Southwestern Medical Center at Dallas, Texas, USA

University of Washington Genome Center, Seattle, WA, USA

Whitehead Institute for Biomedical Research, MIT, Cambridge, MA, USA

Washington University Genome Sequencing Center, St. Louis, MO, USA

So far, the project is ahead of schedule: 94% of the "rough/working draft sequenee" (eovered later) of the human genome has already been completed by the international consortium and is available free online in the GenBank database (see http://www.ncbi.nlm.nih.gov and http://www.ebi.ae.uk).[2] In addition, the "finished sequenees" (explained later) of chromosomes 21 and 22 have already been completed.[3,4] The finished sequenee of the entire human genome is expeeted to be completed by 2003 and will be made freely aeeessible to the public with no strings attaehed.[5] It will join more than 30 other genomes that have already been sequeneed, ineluding the model organisms *Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans, Drosophila melanogaster,* and *Arabidopsis thaliana* (see http://www.ncbi.nlm.nih.gov).

However, Celera Genomics, a private eorporation headed by Craig Venter, who ineidentally is aeeredited for initiating the development of Expressed Sequenee Tags (ESTs), has been eompeting with the international consortium to sequence the human genome[1] (An EST is a single raw sequenee read of a random eomplementary DNA elone). At one point, there was great eoneern that Celera Genomies would eomplete the sequenee of the human genome first with its "whole-genome shotgun sequeneing method," even though it only started in 1998. The concern was that although Celera promised to release the sequenee for free, it had also planned to sell access to a customized database to pharmaceutieal elients. In addition, Celera has filed preliminary patent applieations for several thousand human genes, despite having stated that it would patent no more than a few hundred human genes. Sueh actions have stirred many debates on the proprietorship of genetie material. Lastly, there was the peripheral issue of Celera's preceived humiliation of the eonsortium, by leaving them with the thankless task of "merely finishing" the sequence.

In the end, neither party won the "raee". In faet, with the eounsel of both American politicians and senior scientists, a ehoreographed annouueement of the compilation of a working draft of the human genome by the international consortium, and the first-ever eomplete human genome by Celera Genomies, was made on June 26, 2000. The event was praised as being monumental by many world leaders, most notably U.S. President Bill Clinton and British Prime Minister Tony Blair, even though the sequenees from both groups were far from "finished" quality.[6]

At the time of this historic announcement, the international eonsortium elaimed to have sequeneed 85% of the genome to working draft standard with eaeh base sequeneed seven times over (i.e., "7x coverage"). Celera Genomies elaimed its sequenee covered 99% of the genome, but at 4.6x coverage.[6] Celera Genomies has sinee stopped sequencing, although it has produced a seeond map by ineorporating data from the publie projeet, leaving the task of finishing the genome to the publie international consortium.[7] Rather, Celera Genomies has switehed its foeus to annotating the genome (i.e., making note of novel and known genes, their biological and disease-related properties, as well as other useful information) in order to create a customized database to be used by paying subseribers. Current subseribers include Harvard University, the Hospital for Sick Children, Howard Hughes Medical Institute, Immunex Corporation, Ohio State University, and many others.[8]

The Two Different Approaches: Hierarchical Shotgun Sequencing Vs. Whole-Genome Shotgun Sequencing

The "hierarchical shotgun sequeneing" method that the international eonsortium uses is a dependable, traditional approaeh derived from and akin to the pioneering work of the previous genome sequencing ventures.[5] First, a genome-wide genetie map is construeted using microsatellites (polymorphic sequences eomposed of variable numbers of the dinucleotide repeat CA), genes, and other unique markers. Then, the entire human genomie DNA is broken down into random fragments of 150–200 kb and eloned into baeteria using baeterial artificial chromosome (BAC) vectors.[5] The genomie DNA being used was derived from blood samples of several volunteers from a diverse population. As a preeaution, the eonsortium solicited approximately 5–10 times as many blood donors as it required and is only using the blood from an undiselosed few of these donors. Thus, even the volunteers themselves are unaware as to whether their sample is being used.[9]

A physieal map of the cloned fragments is then constructed, in which the elones are arranged in overlapping sets to form a continuum (i.e., a "eontig"), using information from the genetie map as well as from ehromosome walking. Determination of the DNA sequence itself is earried out on eaeh seleeted elone. Eaeh elone is subjeeted to "shotgun" sequencing, in which 2,000–3,000 "sequenee reads" are determined at random and assembled automatically with computerized algorithms.[5] The assembled sequence is then released into the public domain as a "working draft sequenee." By definition, eaeh base of the working draft sequence must be sequenced four times on average (i.e., 4x eoverage) to deerease the possibility of errors.[9]

Box 2
Why are there gaps in the genome?

Current theory states that there is only one DNA molecule per human chromosome.[10] Although it is rather unlikely for the case to be otherwise, this theory has not yet been proven definitively because of technical limitations. Nevertheless, if the theory is true, then there are gaps in the genome sequence for only two major reasons.[11]

The first is a statistical gap resulting from the shotgun sequencing methods used by both the International Consortium and Celera (although at different stages of the process). Statistical gaps are closed in a directed fashion, by performing shotgun sequencing that is aimed at regions in which the gaps occur.

The second type of gap occurs when a stretch of DNA refuses to cooperate with the sequencing techniques. It may be incompatible with the bacterial cloning agent and not be cloned Sequences with highly biased base compositions are problematic for sequencing reactions. In addition, sequences consisting of multiple repeated sequences can be problematic for both sequencing reactions and the computer assembly programs. Various different methods requiring both creativity and trial-and-error will be employed to close gaps of this nature.

This is followed by a directed "finishing" phase in which all ambiguities are resolved, and the entire sequence is checked before submission to the public database. As well, every effort will be made to close all pre existing gaps. The only gaps that will remain, however, in the finished sequence will be from regions that are impossible to clone or sequence by current methods (see Box 2 for a further discussion of gaps in the sequence). Despite these limitations, the finished sequence will be over 99.99% accurate, partly as a result of being sequenced 9–10 times on average.[9]

Celera is using a different approach, called "whole-genome shotgun sequencing," which was pioneered by Craig Venter himself. It is a much simpler method: the entire genome is shredded into small fragments that are sequenced randomly, by 300 state-of-the-art capillary DNA sequencers (that need almost no human maintenance), and put back together on the basis of sequence overlaps by an $80 million mainframe computer specially built for Celera.[1] The whole-genome shotgun approach is much faster than the traditional strategy being used by the multi-national consortium, because the laborious non-automated creation of genetic and physical maps is not required. However, since whole-genome shotgun sequencing had only been successful for less complex organisms such as bacteria, many scientists were originally skeptical of Celera's ability to piece together the much more intricate human sequence. This skepticism was replaced by mixed emotions when Celera, in collaboration with the Berkeley Drosophila Genome Project, announced in April, 2000 that it had sequenced the *Drosophila melanogaster* genome with its whole-genome shotgun sequencing method.[12] Thus, scientists once skeptical were now worried that Celera might complete its sequencing of the human genome before the international consortium, despite beginning in 1998. The genetic sources for Celera's human genome sequence are three females and two males who had identified themselves, at the time of DNA sampling, as Hispanic, Asian, Caucasian, and African American.[8]

Immediate Functionality of the Human Genome Project

Gene Identification

One of the most immediate applications of the genome project is identifying novel genes. This is usually performed in a two-step fashion, the first of which involves computational analysis. Predictive programs individualized for each organism are available to detect novel genes with the use of a variety of parameters, including codon usage patterns, potential CpG islands, stop/start and splice sites, candidate exons, and others.[5, 13] Novel genes can also be detected with a BLAST (basic local alignment search tool) query based on homology to already known genes.[5, 14, 15] The second step of the novel gene identification process involves confirming the computer-predicted open reading frames (ORFs) experimentally by cDNA sequencing.[5, 14]

Furthermore, the genome sequence serves as an additional database, on top of the current EST databases, to search and pull out novel genes based upon the sequences and weights of proteins and/or peptides derived from mass spectrometric analysis.[13] Locating and cloning full length genes corresponding to interesting mRNA candidates from expression profile experiments on gene chips will also be made easier by having the genome sequence on hand.[16] Nonetheless, scientists conducting "forward genetics" research are not the only beneficiaries of the genome project's results. The genome sequence can also greatly aid positional candidate cloning of disease-associated genes – so called "reverse genetics."

It has been estimated that the human genome contains between 35,000 and 150,000 genes.[7] Evidence for the genome containing as few as 35,000 genes stems from the low number of genes identified by prediction programs run on the "finished" sequences of chromosomes 21 and 22, at 225 and 545 genes, respectively.[17] However, important caveats to this low-end prediction include: (a) chromosomes 21 and 22 when combined represent only 2% of the entire human genome; (b) gene distribution is heterogeneous within the genome; (c) gene prediction programs are continually being improved (and gaining additional sensitivity and specificity).[17]

Comparative Genomics

Another immediate application of the genome project is comparative genomics. Comparison of genomic sequences amongst different species can be used to identify sequences that have been conserved during evolution. Homologs, orthologs, conserved functional domains, conserved control sequences, and novel genes can be identified in such a manner.[14] (Homologs are genes in two or more species that share a common function and origin; orthologs are genes in two or more species that share a common origin, but whose sequences and functions have diverged somewhat following speciation). Additionally, finding differences between organisms can contribute to our understanding of biological functions of genes.

On top of this, there have been new developments in comparative genomics that provide information on the "functional linkages" between proteins. Functional linkage is an expanded view of protein function, in which a protein is defined as an element in the network of its interactions (e.g., components of a transcriptosome complex), as opposed to the classical view of protein function, which focuses on the action of a single protein molecule (e.g., catalysis of a specific reaction).[15] Various terms have been coined for this expanded notion of function, such as "contextual" or "cellular" function. The new developments all involve computational methods that have been tested with proteins that are already known to function together on the basis of experimentation.[15] These methods include Phylogenetic Profiling, the Gene Neighbour Method, Gene Order, and the Rosetta Stone method.

A Phylogenetic Profile describes the pattern of a particular gene's presence across a set of organisms whose genomes have been sequenced.[15] If two proteins have the same phylogenetic profile (i.e., the same pattern of presence or absence) in the surveyed genomes, it is inferred that the two proteins have a functional link. The logic is that proteins that are always inherited together into a new species, function together. The power of this method is best appreciated when the number of possible phylogenetic profiles is considered: since each gene can be either present or absent in each genome, and because there are currently more than 30 fully sequenced genomes, there are 2^{30} ($\sim 10^9$) possible phylogenetic pro-

files. This number far exceeds the number of protein families; thus, a protein's phylogenetic profile is almost always a unique characterization of its pattern of distribution amongst genomes, making it unlikely for any two genes to be erroneously functionally linked by chance using the phylogenetic profiling method.[15]

The second computational method is the Gene Neighbour Method, also known as "synteny".[15] If the genes that encode two proteins are neighbours on a chromosome in several genomes, then the proteins tend to be functionally linked. Functional linkage within the Major Histocompatibility Complex (MHC) locus is a case in point for the utility of the gene neighbour/synteny method.

Gene Order, the third computational method, is a slight variation of the theme detailed above.[15] If the genes that encode several proteins are in a certain order on a chromosome in several genomes, then the proteins are quite likely to be functionally linked. The ß-hemoglobin locus and homeotic gene complex (HOM-C) are examples that support the validity of the theory behind the gene order method.[18, 19] Gene order is conserved in both cases, because it plays a key role in regulating gene transcription in a coordinated fashion, such that the gene products can act together in a synchronized manner.[19, 20]

The fourth and last computational comparative genomics method is the Rosetta Stone Method. This method assumes that if separate proteins A and B in one organism are expressed as a fused protein in another species, then the two proteins A and B are almost certainly linked in function.[15] Thus, a successful search through other genome sequences for the corresponding fused protein is powerful evidence that proteins A and B are functionally linked.

Single Nucleotide Polymorphisms:

Single Nucleotide Polymorphisms (SNPs) are single-base differences in the DNA sequence that can be observed between individuals.[21] The majority of SNPs are single-base substitutions, although deletions and insertions of one or more bases are also observed.[5] These heritable sequence variations arise as a result of either a copying error during DNA replication, damage and misrepair of DNA, or recombination between homologous segments of chromosomes during meiosis in germ cells.[5] SNPs occur, on average, once per 1,000 to 2,000 base pairs in the human genome, and are the predominant basis of genetic variability in the human population, making them the most abundant genetic markers available.[22]

Ten pharmaceutical companies, the Wellcome Trust and a number of other international genome centers have joined to set up a non-profit venture called The SNP Consortium (TSC), to create a library of SNPs that will be made freely available to the public (see http://snp.cshl.org).[23] SNPs can and will be discovered through a variety of fashions, the discussion of which is beyond the scope of this article. Suffice it to say that the availability of the human genome sequence serves a crucial role as a "backbone" with which to relate future SNP discoveries. The TSC estimates that it will have an ordered high-density SNP (>1 million SNPs) map of the human genome completed within the next two years at a cost of over US$45 million.[9, 23] The rationale behind this expensive and time-consuming investment is the current belief that SNPs will be the genetic markers of the next era.

In fact, simply because of their abundance, SNPs have been hailed as the genetic markers that will finally enable scientists to identify the genes that contribute moderating effects in complex traits (also known as multigenic, polygenic, multifactorial, or non-Mendelian traits), by means of linkage disequilibrium (LD) studies (see Box 3 for an explanation of linkage disequilibrium).[22] So far, scientists have only been able to identify genes, by means of positional cloning, for human disorders that present in Mendelian inheritance patterns. These are by their nature rare, and although important to the individuals who carry these genes, are of limited significance in terms of public health.[25] However, the discovery of genes strongly implicated in "multigenic" diseases, such as cardiovascular diseases, diabetes mellitus, autoimmune diseases, cancer and psychiatric or neurogenic disorders, to name a few, has proven elusive. Unfortunately, such multigenic diseases are far more common than Mendelian diseases.

Box 3
What is linkage disequilibrium?

Linkage disequilibrium is an observable phenomenon where a particular haplotype (combination of alleles) of a set of genes and/or genetic markers occurs significantly more or less frequently in a population than would be expected from their physical distance apart, in a randomly mating population.[21]

It is often incorrectly assumed that genes that are physically linked should always show a certain association in the population, i.e., that the chromosomal combinations of alleles *AB* or *ab* occur more frequently than the combinations *Ab* or *aB*. However, this is not the case in a randomly mating population, such as the human species, for the most part. Even if the linkage is fairly close, repeated crossing over across many generations will cause, in the long run, all four combinations—*AB*, *ab*, *Ab*, and *aB*—to be randomly distributed in the population. Thus, as a rule, association of genetic traits does not point to physical linkage. This rule has exceptions, in that some combinations of closely linked genes and/or genetic markers do indeed occur more or less frequently in a randomly mating population than expected given their physical distance apart. This phenomenon, otherwise known as linkage disequilibrium, occurs for one of two reasons: (a) the population under examination originated from a mixture of two populations with different frequencies of the alleles *A*, *a*, and *B*, *b*, and the time elapsed since the populations were mixed has been insufficient for complete randomization; or (b) certain combinations of alleles of physically linked gene loci are maintained in high frequency by natural selection.[24]

Hence, SNPs that are close to, or within, a particular gene variant on a chromosome are likely to be inherited together with that gene variant when they are in linkage disequilibrium. In this way, SNP variations that are in linkage disequilibrium and associated with a disease phenotype can "mark" the position on the chromosome where a susceptibility gene is located.[23] For more information on linkage disequilibrium and the design of linkage disequilibrium studies, please see reference 25.

An individual's response to medication is also a complex trait, governed by a large number of genes.[21, 23] Not surprisingly, the pharmaceutical companies in the TSC hope to use a genetic approach to identify those likely to benefit from medications (i.e., those patients in which there is therapeutic efficacy), and those likely to suffer from side effects and adverse drug reactions (ADRs). Such practice of pharmacogenetics (the study of how genetic differences influence the variability in patient's responses to drugs) has far-reaching medical and economic consequences. Many imagine that sometime in the future, screens of genetic variants using microarray technology will be standardized, so that automated read-outs of each person's predicted response to each medicine could be generated. These DNA-based screens might provide useful information about that individual's drug metabolism characteristics, to aid in the prescription of appropriate medications in appropriate doses.[21] As such, the "trial-and-error" method currently used will be eliminated. Drug development will also benefit greatly; however, this topic is beyond the scope of this article (see reference 21 for details).

Last but not least, "natural" individual variation, in such things as behaviour and physical stature, represents another class of complex traits whose genetic determinants can also be identified with the use of SNPs as markers in linkage disequilibrium studies.[25] Unfortunately, the functional uses of SNPs mentioned above are only theoretical, and as of yet unrealized in any practical manner.[26] Truly high-throughput genotyping technology required for genome-wide population-based studies is still lacking. In addition, a more daunting set of challenges results from our lack of knowledge of the genetic history and epidemiology of SNPs, all of which are required for meaningful linkage disequilibrium studies. Finally, regulations must be developed to guide the ethical use of this new and potentially powerful genetic technology.

Other Genome Projects

The genomes of a number of other organisms are currently being sequenced as well. Celera Genomics has just recently completed its whole-genome shotgun sequencing of three commonly used strains of laboratory mice (129X1/SvJ, DBA/2J, and A/J) with 3x coverage.[5] There is also a Mouse Sequencing Consortium (MSC) that is sequencing another common laboratory mouse strain, C57BL6/J.[27] The rat, pig, zebrafish, and a whole host of viruses, bacteria, fungi, and parasites are also being sequenced. Other animals under consideration include the chicken, pufferfish, and chimpanzee.[28]

Closing Thoughts

The arrival of the human genome sequence has been long-awaited. With it comes many new approaches with which to discover novel genes and further understand protein function. Nevertheless, the long term goal remains the same: to understand the workings of genes so that we can manipulate them for the purposes of disease prevention, management, and hopefully even treatment.

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Addendum

Recently, the International Consortium and Celera have published their results concurrently in *Nature*[29] and *Science*,[30] respectively, along with extensive analyses of the sequences. One of the more interesting results to note is the small number of predicted genes. Computer programs for the International Consortium claim that there are 31,000 predicted genes whereas Celera's claims that there are only 26,000 predicted genes.[29, 30] And, as there are only approximately 6, 000, 14, 000 and 19, 000 predicted genes in yeast, fly, and worm, respectively, this finding has renewed debate and research on the role that genes play in determining the complexity of an organism.[32] Also of note is the fact that a comparison of the quality of the two sequences put out by the International Consortium and Celera is difficult and aimless because different procedures and measures were used to process the data and to estimate their accuracy.[32]

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Acromegaly: A Review and Case Presentation

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Abstract

Acromegaly is a disorder with a wide spectrum of clinical manifestations affecting multiple organs. It is caused by excessive growth hormone (GH) secretion, usually resulting from a benign GH-secreting pituitary adenoma. The effects of GH hypersecretion progress slowly so that the course of the disease is usually insidious. Ultimately, the elevations in GH and insulin-like growth factor-1 (IGF-1) levels, if left untreated, can lead to disfigurement and significant morbidity and mortality. Thus, early diagnosis and treatment are essential in improving patient outcome. Recently, the development of new therapies has allowed for the normalization of GH and IGF-1 levels and reductions in tumour sizes in patients with acromegaly. This review focuses on the current understanding of the pathophysiology of acromegaly, the diagnosis and available treatment options.

Growth Hormone: Regulation, Secretion and Biological Actions

Growth hormone (GH), also called somatotropin, causes the growth of almost all cells and tissues in the body by inducing the production of growth factors, known as somatomedins, which are primarily released from the liver.[1,2] Somatomedin C or insulin-like growth factor-1 (IGF-1) mimics the actions of insulin by inducing protein synthesis, DNA and RNA synthesis, cell proliferation, as well as muscle mass, cartilage and bone growth. In addition to the indirect effects via IGF-1, GH acts directly and has anti-insulin effects. These effects include a decrease in glucose utilization by peripheral tissues, increased hepatic glucose production and hyperinsulinemia, all of which serve to induce insulin resistance in peripheral tissues.[1,2] Other metabolic effects of GH include lipolysis, (which results in a reduction of fat deposition and an increase in fat mobilization) and increased bone mineral density resulting from an increase in calcium absorption in the gastrointestinal tract.[1]

Although GH is not essential for normal intrauterine development and growth, it is an extremely important stimulant of longitudinal growth post-natally. The interaction between GH and IGF-1 produces linear growth during childhood and puberty by inducing chondrocyte proliferation and differentiation at the epiphyseal growth plate. The metabolic effects exerted by GH persist throughout life.[1]

The GH and IGF-1 axis is subject to regulation via multiple internal as well as external cues, such as gender, sleep, age, body composition, nutrition and exercise.[1,3] These cues have a direct effect on the secretion, feedback activity and target tissue actions of GH and IGF-1. There are three primary control loci of the GH-IGF-1 axis; the hypothalamus, anterior pituitary gland and target tissues such as bone, muscle, liver, adipocytes and skin.[1,3]

Hypothalamic Control

Two hypothalamic peptides that reciprocally control GH release have been cloned and sequenced. Growth hormone releasing hormone (GHRH), a 44 amino acid peptide whose neurons are located in the arcuate nucleus of the hypothalamus, acts directly on GH-secreting cells in the anterior pituitary (termed somatotropes) to increase the synthesis and the release of prestored GH.[1,4] On the other hand, somatostatin, which exists as both a 14 and 28 amino acid form, opposes the stimulatory actions of GHRH on GH secretion. This counter-regulation by somatostatin (SS) is due to blocking the pituitary release of presynthesized GH, but not by impeding the synthesis of new GH.[1,4] GHRH and SS neurons (located in the periventricular nuclei) are interconnected both functionally and anatomically. It is widely believed that SS acts not only by blocking GH secretion at the anterior pituitary level, but also by direct intrahypothalamic neuronal inhibitory connections to the arcuate nucleus thereby limiting GHRH release.[1,4,6,7]

Pituitary Control

The anterior pituitary gland receives input (via the portal circulation) from the median eminence, conveying regulatory signals from the hypothalamus. The primary drive to pituitary GH secretion consists of GHRH stimulation of somatotropes in the absence of excessive SS inhibition.[1,4]

Neurotransmitter Control of GH Release

Opioids, cholinergic, serotonergic and dopaminergic inputs are

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stimulatory thereby increasing GH release, whereas catecholamine effects are complex and depend on the receptor subtypes involved. For instance, α-adrenergic neurons are involved in the stimulation of GH secretion, whereas ß-adrenergic neurons inhibit GH secretion.[1,4]

GH and IGF-1 Feedback Mechanisms

IGF-1 and insulin-like growth factor-II (IGF-II) are closely related to insulin in structure and physiological actions. IGF-1, whose secretion is stimulated by GH, has pronounced growth-stimulating activity, whereas IGF-II plays a role in intrauterine growth.[1]

GH is believed to act on hypothalamic sites to increase SS and suppress GHRH, thereby resulting in a decrease in GH secretion. This is referred to as GH autofeedback. Thus far, there has been little evidence to support the notion that GH has direct negative feedback effects at the pituitary level. A recent study by Asa *et al.*[5] has demonstrated synthetic and secretory hyperactivity in pituitary somatotropes of transgenic mice due to reduced GH feedback regulation. This finding is the first indication of the direct inhibitory action of GH on pituitary somatotropes.

In contrast, IGF-1 exerts a direct inhibitory action on GH secretion from the pituitary. In addition, IGF-1 stimulates SS secretion from the hypothalamus. Thus, the GH-IGF-1 axis functions as an integrated "closed-loop" feedback system serving to maintain GH and IGF-1 concentrations within physiological ranges under a variety of external and internal metabolic circumstances.[1,6,7] There are also numerous neurotransmitters that specifically regulate the GH-IGF-1 axis, such as acetylcholine, dopamine, serotonin and opioid peptides, which all increase GH secretion.[1,4,7]

GH Secretion

GH secretion from somatotropes in the anterior pituitary is pulsatile and is largely due to the balance between stimulatory (due to GHRH) and inhibitory (due to SS) inputs from the hypothalamus. The amplitude and frequency of GH pulses are regulated by a variety of physiological factors. There are several lines of evidence suggesting that GHRH is required for the initiation of GH pulses and SS modulates the amplitude of these pulses.[1] GH release is greatest at night, in particular during slow wave sleep.[1]

Acromegaly – Etiology, Prevalence and Incidence

Acromegaly is a clinical syndrome of metabolic disturbances caused by autonomous secretion of GH. As a result of this secretion, there is an elevation in GH and IGF-1 levels. If left untreated, acromegaly can lead to disfigurement, severe morbidity and increased mortality. In fact, there is a 2-3 fold increase in overall mortality in these patients, which is primarily associated with cardiovascular and respiratory disease and malignancy.[2] An overall decrease in survival (by 10 years) is correlated with higher GH levels and the presence of hypertension, diabetes mellitus and cardiovascular disease.

There are a variety of etiologies associated with acromegaly. The causes of acromegaly can be classified as intrapituitary or extrapituitary. Most patients with acromegaly have a GH secreting pituitary adenoma. The intrapituitary causes of excess GH secretion include: densely or sparsely granulated adenomas, mixed somatotrope and lactotrope adenomas, plurihormonal adenomas and GH-secreting carcinomas. Pure somatotrope tumours that secrete only GH account for 60% of all pituitary tumours.[2] The extrapituitary causes of acromegaly can be subdivided into those that result in excess GH secretion, excess GHRH secretion (ectopic tumours) and hereditary acromegaly-related syndromes (such as multiple endocrine neoplasia I). The extrapituitary etiologies combined account for <2% of acromegaly cases.[2]

Epidemiological studies indicate that acromegaly occurs with a population prevalence of 60 per million and an incidence of 3-4 million per year. There are approximately 1700 confirmed cases of acromegaly in Canada.[8] Males and females are equally affected with an average age at presentation of 44 years.[2,10]

Pathogenesis of Pituitary Tumours

Pituitary tumour transforming gene (PTTG) is thought to play a role in pituitary tumourigenesis and has been identified as an estrogen-regulated activating oncogene. The human PTTG family consists of at least 4 genes. Two of these genes are located on chromosomes 5q33 and 4p12. The PTTG gene codes for a securin protein. Overexpression of PTTG causes *in vitro* cell transformation (from normal cell to hyperplastic cell) and induces *in vivo* tumour formation. It has been reported that overexpression of the securin protein leads to the dysregulation of sister chromatid separation. PTTG overexpression occurs in 99% of pituitary tumours and a correlation between the level of PTTG expression and degree of tumour invasion has been reported.[11]

Clinical Manifestations of Acromegaly

Acromegaly has an insidious onset with 10-15 years of GH hypersecretion typically preceding its initial diagnosis. Although the majority of patients have macroadenomas when first diagnosed with acromegaly, approximately 25% of acromegalic patients have microadenomas (<10 mm).[12] Headache, hypopituitarism and visual field defects occur secondary to the expanding tumour. Hyperprolactinemia, occurring in 30% of patients, may be due to the cosecretion of prolactin with GH from the tumour. Hyperprolactinemia subsequently results in amennorrhea, impotence and galactorrhea.[2,12-14]

Facial Changes

There is soft tissue hypertrophy in the face and coarsening of facial features, enlargement of the jaw, tongue, nose and supraorbital ridges. The increase in size of the mandible leads to enlarged interdental spaces distorting the bite. Cartilage proliferation in the larynx leads to voice deepening, severe snoring and sleep apnea, which can subsequently lead to increased somnolence.[2,12-14]

Bone and Joints

New bone formation leads to enlargement of the hands and feet, which can later result in degenerative arthropathy

observed in 70% of all patients. Spinal involvement including osteophytosis and disc space widening can lead to severe kyphosis. Carpal tunnel syndrome, resulting from fibrous tissue thickening, neural enlargement and local fluid retention, is seen in up to 50% of all acromegalic patients.[2,12,14]

Skin Changes

Thickening of the skin, increased facial wrinkling, intensified nasolabial folds and thickened heel pads are observed. Skin tags, also known as fibromata mollusca, may be an indication of the presence of colonic polyps. Patients with acromegaly often have oily skin and hyperhidrosis and may also have acanthosis nigricans.[2,12,14]

Cardiovascular System

Cardiomegaly is almost always present in long standing acromegaly. Arterial hypertension, accelerated arteriosclerosis, ventricular arrhythmia, diastolic dysfunction, ischemic heart disease and left ventricular hypertrophy are frequent manifestations.[2,12,14] The severity of the cardiomyopathy has been found to be correlated with GH and IGF-I levels.[15]

Respiratory System

The thickened lips, enlarged tongue and hypertrophied nasal structures can lead to upper airway obstruction and sleep apnea.[2,12,14]

Gastrointestinal System

Currently, it is not known whether there is altered intestinal absorption of nutrients and minerals in acromegalic patients.[12]

Sexual Functioning

There is loss of libido in >50% of all patients.[12] Hyperprolactinemia seems to be a major cause of acromegaly-related sexual dysfunction.

Metabolic Disturbances

Glucose intolerance and hypertriglyceridemia are the major metabolic disturbances observed in acromegalic patients. In fact, 25% of such patients have diabetes mellitus.[2,12-14]

Malignancy

The most typical neoplastic lesions associated with acromegaly are colonic polyps. The premalignant adenomatous colonic polyps are identified in 30% of patients. Ten percent of patients with acromegaly develop malignant neoplasms including adenocarcinomas of the colon as well as melanomas.[2,12,14]

Other Changes

Soft tissue overgrowth occurs in virtually all patients with acromegaly. There is generalized hypertrophy of soft organs including the tongue, thyroid and salivary glands.[2,12]

Diagnosis of Acromegaly

The diagnosis of acromegaly is based on abnormal laboratory findings in conjunction with abnormal physical examination observations. An increased number of GH pulses per 24 hours is observed in acromegalic patients which is superimposed on markedly elevated basal GH concentrations.[12] Interestingly, the increased GH pulse frequency only accounts for a small portion of the GH secretion in acromegalic patients, which is contrasted with normal subjects in whom >70% of GH secretion is due to the discrete pulses.[12]

Random GH levels are not recommended as criteria for diagnosis due to the pulsatile nature of pituitary GH secretion and the short half-life of GH (20 minutes). In addition, uncontrolled diabetes, malnutrition, renal failure and physical/emotional stress may elevate GH levels.[2,12]

In contrast, serum IGF-I levels do not fluctuate during the course of the day, are not affected by physical exercise or stress and correlate better with clinical manifestations of acromegaly than random GH levels. However, IGF-I levels are affected by nutritional status, age and estrogens. In addition, normal IGF-I concentrations are not necessarily indicative that GH secretion is normal because there are other factors regulating IGF-I secretion, such as liver dysfunction or malnutrition which can decrease hepatic IGF-I production despite high GH secretion.[2,12]

The oral glucose tolerance test (OGTT) establishes the diagnosis of acromegaly when a glucose load of 75 or 100 g following an overnight fast fails to suppress GH levels to <2 μg/L during 1-2 hours. Normally, with oral glucose administration, there is suppression of GH levels to <1 μg/L. In acromegaly, there is not only lack of suppression, there may even be a paradoxical rise following a glucose load.[2,12]

The insulin-like growth factor binding proteins (IGFBPs) are a family of proteins that bind IGF-I and modulate its action in target tissues. IGFBP-3, the major circulating form of IGFBP, binds free IGF-I. This binding leads to an increase in the half-life and biological activity of IGF-I. It has been demonstrated that in untreated acromegaly patients IGFBP-3 levels are elevated. However, IGF-I may be more useful for determining the presence of active disease than IGFBP-3 since IGFBP-3 levels are elevated even in patients with normal OGTT.[12] Although IGFBP-3 levels correlate well with IGF-I levels, IGFBP-3 levels may be in the normal range in up to one-third of patients with acromegaly.[8] Thus, the measurement of IGFBP-3 levels for following disease activity is highly controversial.

There have been other physiological responses observed in acromegalic patients that are not observed in normal subjects. In 50% of acromegalics, there is a rise in GH levels in response to TRH administration and a response to GnRH in a small percentage of patients. The TRH stimulation test has poor specificity as such stimulation is also observed in patients with renal failure, liver disease and depression.[12] Interestingly, there may be a paradoxical reduction of GH following the administration of dopamine agonists in patients with acromegaly despite that dopaminergic agents are normally stimulatory.[12]

Determination of plasma IGF-I levels as well as the GH response to a glucose load are currently the preferred and most cost effective biochemical diagnostic tests. The OGTT also serves as a monitor of long-term response to therapy.[12] It may

become necessary to develop new and more stringent criteria regarding the normal post-glucose GH suppression level due to the increasing use of more sensitive radioimmunometric or immunochemiluminometric assays to measure GH levels.[8]

An MRI of the pituitary should identify any adenoma. If an adenoma is not evident with this imaging modality, ectopic secretion of GHRH should be considered as a cause of excess GH. MRIs used in conjunction with the contrast agent gadolinium-diethylenetriamine pentaacetic acid may provide superior contrast between normal tissues and pituitary adenomas by allowing for visualization of the optic tracts, cavernous sinus and carotid arteries.[2]

Treatment of Acromegaly

Transsphenoidal Surgery

Transsphenoidal surgical resection should be the first treatment modality considered for a well localized GH-secreting pituitary adenoma.[2,8,12,16,17] Following this procedure, sellar compression, hypopituitarism, soft tissue swelling and metabolic abnormalities are restored. Additionally, GH levels normalize within 1 hour and IGF-1 levels usually normalize after 1 week. Despite these immediate results, recurrences (which may reflect incomplete tumour resection) occur in up to 10% of patients. [12,16] Furthermore, a new onset of hypopituitarism with the need for permanent hormonal replacement occurs in 15% of patients.[8,12] The primary reason that pituitary tumours are not cured with surgery is related to the fact that at the time of diagnosis, greater than 70% of patients have a pituitary macroadenoma which extends into the suprasellar space, cavernous sinus, dura mater and bone.[12]

Radiotherapy

Radiation therapy is an option for acromegalic patients that are not controlled by surgery or with medical treatment. Thus, radiation is recommended if GH levels remain elevated following surgery.[2,12,18] The main disadvantage of radiation therapy is the slow rate of response. This means that these patients will continue to have increased morbidity and mortality from elevated GH levels for years following irradiation. Similar to surgery, patients who have undergone radiotherapy can develop hypopituitarism following treatment.[12,18] Secondary intracranial tumours have been reported in 2% of patients within the first 10 years following radiation.[12]

Medical Treatment

Medical therapy is an integral part of the treatment for excessive GH secretion resulting from a pituitary adenoma or from ectopic GHRH secretion. The aim of pharmacological therapy is to reduce serum GH and IGF-1 concentrations and promote reductions in tumour size in some patients. Thus, medical therapy is only effective if it is taken regularly and should be viewed as a treatment rather than a cure.

Dopamine Agonists

Although dopamine agonists, such as bromocriptine, stimulate GH release in normal subjects, they paradoxically reduce GH levels in acromegalic patients.[2,12] There are numerous side effects associated with dopamine agonists, such as nausea, vomiting and orthostatic hypotension. However, these side effects can be minimized by initiating treatment with a low dose and gradually increasing it. The side effects are less common with the long acting dopamine agonists.[12]

Somatostatin Analogs

It is known that SS can alter various physiological responses in the body. Despite this, its clinical use has been limited due to its short half-life of 2-3 minutes and its poor bioavailability. In addition, SS withdrawal causes an excessive amount of GH to be secreted, a phenomenon known as rebound hypersecretion.[19] Research has led to the development of a long-acting synthetic SS octapeptide derivative, octreotide, that is administered subcutaneously. Octreotide contains the core amino acids necessary for receptor binding of SS. Octreotide is stabilized against enzymatic attack, which increases its half-life to 1.5 hours. Octreotide has a 40-fold greater potency than the naturally occurring SS. As well, there is no rebound hypersecretion associated with octreotide withdrawal.[12,20]

Octreotide treatment (usually administered in 3 daily injections) is indicated in several situations: a) acromegalic patients who have responded inadequately to surgery or irradiation, b) those patients who cannot be treated by surgical and/or radiation therapy, c) patients with severe symptoms, including headaches and sleep apnea and d) in post-radiotherapy patients due to the delay in clinical remission following such a procedure.

Octreotide has been shown to rapidly reduce GH secretion and IGF-1 levels as well as having long-term beneficial effects in patients with acromegaly. The signs and symptoms resulting from acromegaly (such as headaches, soft-tissue swelling, arthralgia, fatigue and hyperhidrosis) have been reported to improve in up to 95% of patients treated with octreotide and these improvements are often noted within the first few days following treatment.[21] A randomized multicentre study by Ezzat *et al.*[22] have reported improvements in clinical and biochemical features in 60-70% of patients within several days following initiation of octreotide therapy. However, the repeated injections are inconvenient and may lead to less than optimal compliance for patients on chronic therapy.

Three long-acting injectable formulations, known as octreotide acetate LAR (long acting, repeatable), lanreotide SR and LAN-60 (60 mg), have been developed in order to overcome the need for patients to undergo daily injections. A single intramuscular injection of octreotide acetate LAR and LAN-60 provides sustained release of the drug for several weeks, whereas lanreotide SR is administered every 8-14 days.[21,23]

The effects of octreotide LAR treatment in acromegaly patients are well documented in the literature. Laneranjan *et al.*[24] have reported sustained suppression of GH in all patients treated with octreotide LAR. There was also a marked improvement in the signs and symptoms associated with acromegaly in 47%-81% (total n=101) of treated patients including amelioration of fatigue and carpal tunnel syndrome. A further 36% of the patients became asymptomatic and 72% of the patients moni-

tored for GH secreting adenoma shrinkage experienced a reduction in tumour size of >20%.[22] Although both subcutaneous octreotide and octreotide acetate LAR are well tolerated, there is the potential for asymptomatic gallstones to develop in 10-20% of patients treated with these drugs.[22,24]

Recently, an Italian multicentre study has been undertaken to evaluate the efficacy of LAN-60. Intramuscular injections of LAN-60 were administered every 28 days for 6 months (n=14). After 3 months of treatment, GH levels decreased by >50% in all patients and GH levels were found to be <2.5 μg/L in 5 patients and <5 μg/L in 3 patients. In addition, IGF-I levels were reduced by at least 30% in all patients.[25]

GH Receptor Antagonists

A novel genetically engineered analog, known as pegvisomant, which functions as a GH receptor antagonist, has been developed. SS analogs and dopamine antagonists bind centrally to specific tumour receptors thereby inhibiting pituitary GH secretion. The mechanism of action of pegvisomant is different in that pegvisomant is a mutated GH molecule that prevents receptor dimerization and results in the disruption of intracellular signaling thereby inhibiting peripheral IGF-I generation.[26-28]

Treatment with pegvisomant for 12 weeks was reported to have normalized IGF-I levels in 6 patients that were previously shown to be resistant to maximal dose octreotide treatment.[22] However, serum GH levels were increased in 5 of these patients and no change in tumour size was observed during pegvisomant therapy. Increases in serum GH during a 12 week treatment regimen with pegvisomant and normalization of IGF-1 levels in 92% of patients treated with pegvisomant for up to one year have been reported in another study by Trainer *et al.*[29] Since GH receptor antagonists do not act by binding to the pituitary tumours, a potential risk for increased GH secretion exists in that the negative feedback from IGF-I is lost.[8] Despite the uncertainties associated with the long-term safety and efficacy of pegvisomant, GH receptor antagonists represent a novel therapeutic approach in the treatment of acromegaly.

Therapeutic Goals

The therapeutic goals in acromegaly are to reduce morbidity and mortality so that these rates are comparable to the expected age and sex-adjusted rates. Treatments should be safe and aimed at removing the tumour or controlling its growth and restoring GH secretion and action to normal. With regards to biochemical parameters, the goals are to reduce serum IGF-1 levels to normal (adjusted for age and sex) and to reduce serum GH levels to <1 μg/L following OGTT. GH levels appear to be the single most important determinant of mortality in acromegalic patients.[29]

Case Presentation

In 1992, a 60 year-old male was noticed by his family doctor to have enlarged hands and nose. For the previous 10 years, the patient had noticed that his hands were enlarging, but he did not feel that there had been any appreciable change in his facial features. Head and neck exam revealed course facies and a prominent supraorbital ridge. There was a decreased visual field in the left eye. The skin of his palms and soles was noted to be very thick. The rest of the physical exam was unremarkable. His blood glucose level was elevated on routine blood work.

Subsequently, an MRI revealed a pituitary macroadenoma. A diagnosis of acromegaly was made and the patient underwent transsphenoidal surgery where 30% of his tumour was debulked. Surgical pathology and immunohistochemistry confirmed the diagnosis of pituitary adenoma with a positive stain for GH and negative stain for prolactin, TSH, ACTH, FSH or LH.

Post-operatively, the patient's GH and glucose levels normalized. However, his testosterone and gonadotrophin levels were low. A diagnosis of secondary hypogonadism was made and testosterone replacement with delatestryl was initiated. The patient was closely monitored on a yearly basis both radiographically and biochemically.

An MRI performed in 1997 indicated that there was no compression of the optic chiasm although residual tumour involving the left cavernous sinus was noted. In 1998, the patient's GH levels and IGF-1 levels were found to be elevated and the patient reported a decrease in energy and an increase in the frequency of headaches. The radiation oncologist suggested medical therapy instead of radiotherapy. Octreotide LAR therapy was advised due to the fact that the patient's prolactin levels were in the normal range.

The patient responded promptly to octreotide therapy with no significant side effects. Both IGF-1 and the GH response to a glucose load were normalized with a GH level < 0.3 μg/L at 2 hours during an OGTT.

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Assessing Health-Related Quality of Life

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Abstract

In the provision of medical care, patient outcomes and treatment preferences are often inadequately assessed. One possible approach is the usage of health-related quality of life (HRQoL) measurements and utility theory. Utility theory is a mathematical construct that quantifies patients' HRQoL by assessing their desirability of being in a particular state of health. The standard gamble (SG) and time trade-off (TTO) methods of utility assessment provide clinical tools for analyzing patient desirability for their current health state both prior to and post-treatment. This article will review the theoretical foundation of the utility assessment tools and their application in the clinical setting.

Quality of Life

The World Health Organization (WHO) defines quality of life (QoL) as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[1] It is affected by factors such as an individual's physical and mental health, level of independence, social relationships, and his/her relationships to salient features of the environment.[1b] In patient care, issues surrounding QoL impact on resource allocation and choice of treatment modalities.

Physicians find themselves in complicated decision-making situations that are often compounded by inaccurately considering their patients' desires with respect to treatment.

This is especially true in the chronic medical patient. The current literature indicates that patients' feelings, values and opinions cannot be assumed.[1] How is a physician to effectively assess the health-related quality of life of his/her patients?

Health-Related Quality of Life

A simple method of clinically assessing patients' health-related quality of life is required. Health-related quality of life (HRQoL) focuses on the effect of a patient's health state on his/her ability to live a fulfilling life.[1] It is distinct from obtaining information on QoL, which includes adequacy of housing, income and perceptions of the immediate environment. HRQoL has been further defined as an optimum level of mental, physical, role (work, parenting, etc.) and social functioning, including functioning in relationships, and perceptions of health, fitness, life satisfaction, and well-being.[1] Knowledge of a patient's HRQoL would be invaluable in tailoring treatment modalities, providing medical management and assessing outcomes of health status.

Utility

Several different tools can quantitate HRQoL, but if one desires to compare patients for example, one requires a standardized measurement approach that is both reproducible and valid. Utility measurements are one such approach.[2] Utility is defined as the desirability or preference that patients exhibit for their health state. Utility theory is based on economic theory; it is a method of decision-making based on a set of axioms of rational behaviour.[3] It enables a decision-maker to proceed in a manner consistent with his/her fundamental preferences. It also allows for quantification of preferences of treatment alternatives, so it may be particularly effective in medical decision-making and in clinical trials. Finally, the theory provides a method of measuring health benefits in general units,[4] facilitating treatment priorities and resource allocation.[5]

Utility Measurement

The concept of using utility measurements as indicators of patient preference is derived from the need of society to assess the effectiveness of its health care. Utility therefore reflects a patient's desirability for a particular state of health.[6] Utilities can be derived for different health states by eliciting patients' relative preferences for various health states. The values obtained may be aggregated to create a mean population value for a certain illness or treatment and thereby serve to prioritize resources. Furthermore, the values obtained reflect the essence of a disease state in a more effective manner than any one particular statistical tool.

In measuring utility, it is important to explain to the patient that all treatment and outcomes will be without expense[7] to ensure that the utility measurement serves as an index of HRQoL. Health states or health state outcomes represented as utility are numbers on a scale where death is given a 0.0 value and per-

fect health (life free of any disease process), a 1.0 value.[7] In order to simplify the discussion, states worse than death (negative integers) will not be considered. Table 1 illustrates various health states and their respective utility values. How these utility values were reached will be discussed.

Table 1
Utilities for Various Health States

Health state	Utility
Healthy (reference state)	1.00
Kidney transplant (TTO-patients)	0.84
Some physical and role limitation with occasional pain (TTO-gp)	0.67
Home dialysis (TTO-patients)	0.64
Home dialysis (TTO-gp)	0.54
Anxious/depressed and lonely (TTO-gp)	0.45
Being blind or deaf or dumb (TTO-gp)	0.39
Dead (reference state)	0.00

Adapted from reference 8.
Utility is assessed by the general public (gp) or patients via the time trade-off technique (TTO). The value of the healthy state has a utility of 1.00 and death has a value of 0.00. All other utilities are determined relative to these two states.

The utility approach is both valid and useful in assessing HRQoL. Applications are readily apparent and may include clinical analysis for individual patients, clinical trials, comparative analysis of populations, and economic evaluations of the cost-effectiveness of alternative medical treatments.[4] In conducting economic appraisal, individual utilities may be aggregated into a collective social utility.[7] In this method of cost utility analysis, aggregation between subjects is achieved by measuring all individual utilities on the common 0.0-1.0 scale and taking the arithmetic mean to arrive at a population or societal value.[7]

Utility Measurement Tools

1) The Standard Gamble

The Standard Gamble (SG) is founded in the fundamentals of utility theory. It is used as an instrument for measuring utilities and preferences.[5] It involves a choice between two options. Subjects are told that they may keep their own health state or achieve full health status for the remainder of their lives (e.g. in relation to a specific treatment choice).[7] The alternatives are therefore two possible outcomes for a given treatment; a good outcome with probability p (full health with a utility value of 1.0) and a bad outcome with probability 1-p (death and its utility value of 0.0). The patient also has the choice of their current health status, which has a certain outcome intermediate between full health status, and death. The value of p is therefore varied until making the choice between continuing in the current health status and gambling on the proposed treatment is an indifferent decision for the subject, at which point the utility value may be calculated by simple arithmetic. Thus, p represents the utility value of the health state.

Hypothetical Clinical Interaction Between A Clinician (C) And Patient (P), Illustrating The Use Of The Standard Gamble Technique Of Utility Assessment

C: I would like to ask you some questions about your current state of health. How has your illness impacted on your life?

P: The loss of my sight has stopped me from reading and driving, and I've even had to stop working.

C: What if I told you about a new and free medical treatment that would allow you to be in perfect health, free from your illness and its complications? Sometimes however, the treatment fails. If this happens, death is certain.

P: This new treatment will either restore me to perfect health or kill me in the process?

C: Yes. What I would like to know is the highest risk you are willing to take and still decide on receiving treatment.

P: If it were 80% successful, I would chance it.

C: Where would you have trouble in deciding whether or not to take the treatment?

P: It would be at around 75%. If the treatment were only 75% successful, I would do it. If it were 70% successful, I would not do it.

C: If your risk of dying were 1 in 5 you would try the procedure, but if it were 1 in 4 you would refuse.

P: Yes.

C: Thank you for your time.

This example illustrates a utility for the health state of 0.75. Calculation: bad outcome = 1 – good outcome (with probability p); $0.25 = 1 - p$, therefore, $p = 0.75$

2) The Time Trade-Off

The second method of assessing utility is the Time Trade-Off (TTO) technique. A patient is asked to consider their health state extrapolated over a fixed period of time. This technique avoids the use probabilities, as in the SG, which may be confusing.[4] The subject is presented with two alternatives and asked to select that which is preferred. The first choice offers a particular outcome for a specified length of time, while the alternative offers a different outcome for a different length of time.[5] For example, a new theoretical treatment will give a subject normal health for a shorter period of time, but he or she

will probably die or be severely disabled at the end of that time. The person is subsequently asked to "trade-off" the time with reduced capacity for living with normal health for a shorter period of time. The time spent in normal health is varied until the point of indifference is found between the two health states.[1] It is only logical that the less desirable health state will result in a greater amount of life traded-off by the subject in order to be free of the health state. When the indifference point is found, the utility for the health state can be easily calculated, given that if the patient is willing to trade all his/her life away, the value of that health state (the patient's current health state) is 0.0, and if the patient is in a state of health in which no time would be traded off, that health state has a utility value of 1.0.

Hypothetical Clinical Interaction Between A Clinician (C) And Patient (P), Illustrating The Use Of The Time Trade-Off Technique Of Utility Assessment

C: May I ask you some questions about your illness and its impact on your life? How long is it that you expect to live given your current state of health?

P: Since I'm 30 now, I think I may live to 80.

C: For the next 50 years, do you expect to have your current illness?

P: Yes, unless a cure or treatment is discovered.

C: Let me say that there is a new and free procedure that could cure this illness for the rest of your life. The only problem with this treatment is that it shortens your life. What is the maximum amount of years you are willing to consider trading in order to improve your current quality of life?

P: I would say that I would trade-off 5 years.

C: When is it most difficult to decide?

P: Well I know that I would definitely trade-off 5 years of my life, but definitely not 10 years.

C: Living with your illness and the threat of complications for 50 years is almost the same as living 45 years without the disease.

P: Yes, I would say that.

C: Thank you for answering these questions.

The previous example illustrates a utility for the patient's health state of 0.90.

Discussion

Subjects find the TTO questions to be the simplest to answer, while the SG methodology is more difficult.[4] In general, interviewers find all techniques easy to learn and administer.[7] It should be noted that the application of the SG may prove to be difficult for the elderly and poorly educated patients. It can therefore become relatively time consuming to administer.[5] Furthermore, physicians may be hesitant to apply these techniques to those with terminal or poor prognostic diseases, such as cancer, because of the obvious references to death and treatment failure.

The SG technique is accepted as the standard for utility measurement.[3] Although somewhat complex to administer, it may be applied by trained interviewers on educated subjects.[3] Reliability is acceptable for this measurement instrument, especially when used in determining population mean values. Internal reliability is 0.77 and one-year test-retest reliability yields a coefficient of 0.53.[1]

The TTO is, however, a tool that subjects find easy to understand.[4] Reliability, both internal and one year test-retest, is slightly better than the SG's reliability, although the difference is statistically insignificant. Internal reliability is 0.79 and one-year test-retest reliability is 0.62.[1] For population mean values, the TTO technique appears to give equivalent results to the standard gamble technique, and the relationship between measures obtained from these two instruments is given by the function of SG=TTO.

A study by Torrance (1976) using randomly selected samples and covering a cross-section of health states for both sexes and all ages indicated the TTO as the method that is best suited for use on the general public. The TTO method gave similar results to the SG. In addition, it was somewhat simpler and slightly more reliable to use.[5]

The current literature has made use of HRQoL as an outcome measure of both disease progression and surgical treatments. In a recent 1999 study by Tillinger *et al.*, a cohort of 16 patients were assessed with the TTO and traditional HRQoL outcome measures of inflammatory bowel disease for response to surgery in Crohn's disease. The authors concluded that over a 24-month post-operative period, the TTO method of outcome assessment was valid in providing an accurate assessment of HRQoL. Hence, a drop in HRQoL as measured by the TTO method might be considered as an indication for surgery in Crohn's disease.[9]

In another study,[10] the TTO and SG methods of HRQoL assessment were compared for validity and reliability with the traditional SF-36 health survey in a group of 25 patients with systemic lupus erythematosus (SLE). It was concluded that the TTO was both valid and reliable in these patients. The SG method was of questionable usefulness because of its poor correlation to the SF-36.[10] The study concluded that the TTO had a future role in the evaluation of new therapies in SLE patients, given the desire to minimize the cost (of treatments) to utility ratio.[10]

Conclusion

It can be appreciated that the TTO and SG methods of assessing utility or HRQoL are of clinical significance to both surgical and therapeutic management. The ease with which these tools may be applied facilitated their subsequent usage in characterizing patients' health states, and compared favorably with laboratory or traditional methods of clinical assessment. Furthermore, the TTO and SG provided an effective manner by which patient preferences regarding treatment modalities may be determined. The standard gamble and time trade-off methods of utility determination were also able to quantitate patient preferences and subsequent outcomes. With further research into this area, improvement in patient care and resource allocation for health will be the net result.

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Crohn's Disease in Children

Kiran K. Kundhal, (0T1)
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Anne M. Griffiths,* M.D., FRCP(C)

Abstract

The diagnosis of Crohn's disease is based on clinical presentation, radiographic criteria and exclusion of other causes. Biopsies of specimens are supportive. Non-diagnostic tests such as ESR reflect disease activity. Small bowel follow-through is used to investigate small intestinal disease. Colonoscopy is employed to evaluate the large bowel. The incidence of Crohn's disease has been increasing in all age groups in most Western societies; the onset is most commonly during late adolescence or young adulthood, with a small peak in the 6th decade. Pediatric Crohn's disease is more common in males. Whites and Ashkenazi Jews are especially prone to Crohn's disease. The pathogenesis of Crohn's disease likely represents an interaction between genetic factors, exogenous triggers and modulating factors. Various infectious, dietary and environmental factors have been suggested as causative agents. The most accepted theory postulates a dysfunctional immune response to bacterial antigens. Crohn's disease is a panenteric entity with defects found throughout the gastrointestinal tract. Defects tend to be segmental and separated by normal areas of intestine. Presenting symptoms may be non-specific; however, the classic presentation consists of abdominal pain, diarrhea and weight loss +/- extra-intestinal manifestations. Both pharmacological and surgical interventions are utilized to decrease inflammation.

Introduction and Epidemiology

Crohn's disease is a type of Inflammatory Bowel Disease (IBD) of uncertain etiology. It is a chronic, transmural inflammation that can affect any portion of the gastrointestinal tract. The terminal ileum is most frequently involved. Approximately one-third of cases involve primarily the colon, one-third the ileum alone, and one-third both the ileum and colon.[1] Rarely, the proximal small bowel, stomach, or mouth may be involved.[1] The clinical course of Crohn's disease is commonly marked by unpredictable exacerbations.[2] The incidence of Crohn's disease is 2 per 100,000, with 20% of all patients being children or adolescents.[2,3] In this review, we discuss the diagnostic methods, epidemiology, etiology, pathogenesis, pathology, clinical presentation and treatment of Crohn's disease with specific reference to the pediatric population.

Descriptive Epidemiology

Between the 1950s and 1980s, the incidence of Crohn's disease increased significantly in all age groups in most Western societies. The incidence of Crohn's disease doubled among Welsh children between 1983 and 1993,[3] and tripled among Scottish children between 1968 and 1983; a similar increase was also reported between 1981 and 1992 in Scottland.[4,5]

Geographic Trends

Crohn's disease is most prevalent in North America, Northwestern Europe, and the United Kingdom;[6] it is less prevalent in Southern Europe, South Africa and Australia, and rare in Asia, Africa and South America. A European study of prospectively accrued cases revealed that the incidence of Crohn's disease is slightly higher in northern regions.[7] Crohn's disease has become more common than ulcerative colitis, a different form of Inflammatory Bowel Disease, in parts of North America and the United Kingdom.[6,7]

Age and Gender Trends

Crohn's is a disease of late adolescence or young adulthood, with peak incidence in the second and third decades of life; there is a second smaller peak in the sixth decade.[6] Overall, the disease is 20–30% more common in females,[6] but studies confined to pediatric-onset Crohn's disease demonstrate a male predominance.

Ethnic Group Trends

Whites are more commonly affected than blacks.[8] Individuals

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of Jewish descent, particularly Ashkenazi Jews, are especially prone to inflammatory bowel disease.[9]

Genetic Factors

The pathogenesis of Crohn's disease most likely represents an interaction between genetic factors, exogenous or endogenous triggers, and modulating factors. An afflicted first-degree relative is currently the major identified risk factor for the development of Crohn's disease.[10] One Swedish study reported a higher (44.4%) concordance for Crohn's disease among monozygotic twins than dizygotic twins (3.8%).[11] Heritability, which describes the relative importance of genetic versus environmental factors, is expressed as the ratio of the prevalence among siblings to the prevalence in the general population, and is represented by λs.[10] In Crohn's disease, λs ranges from 10 to 35,[10] implying that the relative contribution of genetic factors in Crohn's disease is greater than in schizophrenia, asthma or hypertension.[10]

Crohn's disease tends to occur at a younger age in offspring than in affected parents.[12,13,14] In several neurologic disorders, such as Huntington's Disease, this tendency for a disease to develop at an earlier age with increased severity in succeeding generations is due to an increased number of trinucleotide repeats in the causative gene. Whether the onset patterns of familial Crohn's disease are reflective of a "genetic anticipation" mechanism (like trinucleotide expansion) is unknown. Earlier exposure to environmental triggers and ascertainment biases constitute alternative explanations. The ascertainment bias may exist because these children are likely to be monitored for disease presentation.[12,13,14]

The number of genes contributing to Crohn's disease is not known at the present time.[9] Some investigators believe that a major autosomal recessive gene may account for a proportion of Crohn's disease, particularly early-onset disease.[15] However, it is more likely that several genes are responsible.[10] Linkage studies using DNA from affected sibling pairs and their parents have identified several chromosomal loci now suspected to contain IBD susceptibility genes.[16]

Infectious Agents

Environmental factors appear to be important in the development of Crohn's disease, as evidenced by the increased incidence in recent decades[6] and the lack of complete concordance among monozygotic twins.[11,17] An infectious agent responsible for triggering Crohn's disease is possible and a number of such agents have been studied. *Mycobacterium paratuberculosis* is known to cause Johne's disease, an intestinal disorder in ruminants that is similar to Crohn's disease. However, similar Mycobacterium species have been cultured from relatively few patients with Crohn's disease.[18]

Wakefield and others postulated a viral etiology for Crohn's disease by demonstrating evidence of persistent measles infection in foci of granulomatous vasculitis in patients' intestines.[19] Wakefield proposed that an early infection with measles may lead to microvascular thrombosis, multifocal gastrointestinal infarction, and eventually gross pathologic sequelae.[20] This hypothesis is supported by a report of three cases of advanced Crohn's disease in the children of three of four mothers afflicted with measles during pregnancy.[21] However, other scientists have been unable to identify persistent measles infection by immunohistochemical staining of tissue from Crohn's patients.[22,23]

Dietary Factors

Person *et al.* examined studies that described the reported premorbid intake of refined sugar, cereals, fiber and milk products in Crohn's disease patients and controls.[24] An increased pre-morbid intake of refined sugar has been reported repeatedly in the studies they examined. However, the study designs failed to account for the possibility that this was a behavioral adaptation to the disease rather than a cause of the disease.[24] A correlation study from Japan showed that the increasing incidence of Crohn's disease paralleled increasing daily intake of animal protein, total fat, animal fat and especially certain polyunsaturated fatty acids (PUFAs).[25]

Environmental Exposures

Early life events may influence the risk of developing Crohn's disease.[26,27] For instance, the risk of Crohn's disease may be reduced by breastfeeding. Later in life, smoking is a clear risk factor, with a point estimate (odds ratio) between 2 and 5. Cigarette smoke has been shown to cause morphological injury to endothelial cells, thereby leading to microthrombi formation.[28] The risk for former smokers does not differ from the risk in people who have never smoked. This suggests that smoking is a promoting rather than initiating factor in the development of Crohn's disease. Smoking is not very common among young children, but should be considered a factor among teens.[28] Although oral contraceptive use has been implicated as a risk factor in the development of Crohn's disease, risk estimates are low, and in certain studies an increased risk has only been found in subsets of patients who smoke.[29] The use of oral contraceptives is most common among 20–29 year-olds but should also be considered as a potential risk factor among sexually-active teens.[30]

Pathogenesis

The most accepted theory with respect to the pathogenesis of Crohn's disease postulates a dysfunctional immune response to bacterial antigens caused by a mucosal barrier defect, an antigen-processing defect, or an immunoregulation error. There is significant evidence pointing to the role of commensal enteric bacteria in the initiation and propagation of Crohn's disease.[31,32,33] Transgenic animal models of Inflammatory Bowel Disease have shown that inflammation is

prevented and or lessened in the presence of a germ-free environment.[34]

Convincing evidence suggests that excessive permeation of bacterial and other luminal antigens across the epithelium plays a major role in propagating Crohn's disease; however, it is unknown whether this defect is primary or secondary.[35,36]

Pathology

Crohn's disease's gastro-intestinal defects tend to be segmental and separated by normal areas of intestinal morphology. Studies performed at the Hospital for Sick Children in Toronto evaluated the initial presentation of Crohn's disease via small bowel radiography and colonoscopy. It was found that 29% of children had terminal ileal +/- cecal disease, 9% had mostly proximal involvement (ileal or jejunal disease), 42% ileocolonic inflammation, and 20% colon involvement only.[37]

The aphthous ulcer is the earliest lesion in Crohn's disease, occurring over Peyer's patches in the ileum and over lymphoid follicles in the colon. The ulcers tend to enlarge with disease progression, and surrounding islands of nonulcerated mucosa give the classic "cobblestone" appearance seen on colonoscopy. Examined grossly, specimens of bowel affected by Crohn's disease exhibit marked wall thickening and luminal narrowing. The mesentery tends to be thickened in such a manner that the intestine is fixed in one position. Associated mesenteric lymph nodes are commonly enlarged. Transmural inflammation may cause intestinal loops to be matted together and fistulas to adjacent structures to form. "Skip lesions" are seen both grossly and microscopically as mucosal inflammation interspaced with normal mucosa.[38]

Microscopically, the presence of fibrosis and submucosal histiocytic proliferation is highly suggestive of Crohn's disease, with the trademark of transmural extension to all layers of the bowel wall and adventitia.[39] Granulomas have been found in 60% of surgical specimens and in only 20-40% of mucosal biopsies; when present, they are more often found in the submucosa than the mucosa.[39,40] They may also exist in other areas such as the peritoneum, mesentery and lymph nodes.[39,40]

Clinical Presentation

The presenting symptoms may be relatively nonspecific, such as abdominal pain or weight loss; Crohn's disease may present with an isolated finding like anemia. One must perform a careful history and physical examination in order to detect typical findings of Crohn's disease in the pediatric population. Typical findings include a plateau in linear growth, delayed pubertal development, perianal lesions and clubbing. The classical presentation consists of abdominal pain, diarrhea, poor appetite and weight loss +/- extraintestinal manifestations; of these, abdominal pain is the most common, followed by diarrhea. This symptom complex is found in nearly 80% of children and adolescents who are diagnosed with Crohn's disease.[2] Patients may also present with short stature and delayed sexual maturation, findings which may precede intestinal symptoms. Affected children tend to have a normal weight for their height, but a low height for their age.[41]

Perianal lesions, including fistulae, tags and recurrent abscesses, may be isolated presenting signs of Crohn's disease.

Extraintestinal manifestations may also accompany Crohn's disease; common sites include the skin, joints, liver, eyes, and bones.[42,43] Twenty-five to thirty-five percent of adult patients with inflammatory bowel disease have at least one extraintestinal manifestation.[42] Patients with colonic involvement are more likely to have extraintestinal manifestations than patients with isolated small intestinal lesions.[42,43] Arthritis is the most common extraintestinal feature of Crohn's disease, typically involving a few large joints, such as the knees, hips and ankles.[42,43] Erythema nodosum and pyoderma gangrenosum are the most common skin lesions.[43] Erythema nodosum tends to occur during periods of active disease, whereas pyoderma gangrenosum tends to occur independently of disease activity, thereby making treatment more difficult.[43] Although ocular lesions are less common in the pediatric population than in adults, acute episcleritis, uveitis and orbital myositis are known to occur.[43,44] Primary sclerosing cholangitis (PSC) may occur in Crohn's disease involving the colon, and acute pancreatitis may rarely occur as well.[45] Renal complications include ureteric obstruction, hydronephrosis, and calculi.[46] Vascular complications, including deep vein thrombosis and pulmonary embolism, have occurred in patients with Crohn's disease and are thought to be related to elevated factors V and VII, and inhibition of antithrombin III.[47] Finally, decreased bone density may occur in Crohn's disease and is attributed in part to the inhibition of bone formation by cytokines.[48] One recent study found that 25% of newly diagnosed children had bone densities in the osteoporotic range, even prior to corticosteroid treatment.[49]

Diagnostic Method

The diagnosis of Crohn's disease is typically based on clinical presentation, radiologic appearance of the small bowel, endoscopic or radiologic appearance of the large bowel and exclusion of other causes of chronic inflammation. Mucosal biopsies are usually supportive. Stool cultures may exclude infectious diseases such as Salmonella, Shigella, Campylobacter and *Clostridium difficile*.[2]

Non-diagnostic laboratory tests are often used to track disease activity. The erythrocyte sedimentation rate has typically been used to screen for inflammation. It is more commonly ele-

vated in Crohn's disease than in ulcerative colitis. Recently, the acute phase reactant serum orosomucoid has been shown to more accurately reflect disease activity.[2]

Small bowel follow-through, which is a barium study of the small intestine involving the use of X-rays to follow barium through the small bowel, is the routine method for investigation of small intestinal disease. Visualization of the small intestine during small bowel follow-through is improved via insufflation of air per rectum.[2]

Colonoscopy is the preferred method for initial evaluation of the large bowel because of its sensitivity in identifying mucosal inflammation. In addition, mucosal biopsies can be obtained easily during the procedure.[2]

Treatment

In treating patients with Crohn's disease, pharmacological and, where appropriate, surgical interventions are utilized to minimize mucosal inflammation and thereby alleviate symptoms. Concurrent with administering treatment, the physician considers measures aimed at optimizing growth, normalizing pubertal development, fostering normal social development and avoiding long-term disease related complications.[37]

One of the indices of therapeutic success is normalizing growth. Adequately treating intestinal inflammation and at the same time providing adequate nutritional intake are of great importance in minimizing or preventing growth impairment.[37] Numerous drugs are used in the treatment of pediatric Crohn's disease; these have been summarized by their activity and anatomical location of action in Table 1. It is beyond the scope of this paper to discuss pharmacological therapy in depth.

Timely intestinal resection is an important part of the optimal management of pediatric Crohn's patients. Surgery is recommended when symptoms persist despite medical therapy or in the presence of intestinal complications, including obstruction, entero-vesicular fistula, intraabdominal mass and, less commonly, free perforation or intractable hemorrhage. Often, by the time resection is performed, many children have already experienced linear growth retardation, an indicator of medical therapy failure.[37]

Summary

Crohn's disease is not uncommon in the pediatric population. Clinicians may promote early identification by considering epidemiological data, ethnic trends, family history, and macro-

Table 1

Pharmolcologic Treatment of Pediatric Crohn's Disease

Disease Location	Treatment of Active Disease	Maintenance of Remission
Small bowel only	• Corticosteroids: prednisone • Oral 5-ASA* (Pentasa or Salofalk most suitable) • 6-MP** • Azathioprine • Sulfasalazine	• Oral 5-ASA • 6-MP/azathioprine
Colon only	• Oral 5-ASA (Asacol or Dipentumn most suitable) • Metronizadole • Corticosteroids: prednisone • 5-ASA enemas*** • 6-MP/azathioprine	• Sulfasalazine • Oral 5-ASA • 6-MP/azathioprine
Ileocolonic	• Same as for *small bowel and colon* as above	• Same as for *small bowel and colon* as above
Perianal	• Metronizadole • 6-MP/azathioprine • Ciprofloxacin	• Metronizadole

Adapted from: Griffiths AM, Inflammatory Bowel Disease. In Gellis SS and Kagan BM. Current Pediatric Therapy 16th ed.
* 6-mercaptopurine ** 5-Aminosalicylic Acid *** no clinical trials

scopic and microscopic appearance of disease. Various diagnostic methods can be employed to confirm a diagnosis of Crohn's disease. Numerous treatment options are available for Crohn's disease, but no cure is foreseen in the near future.

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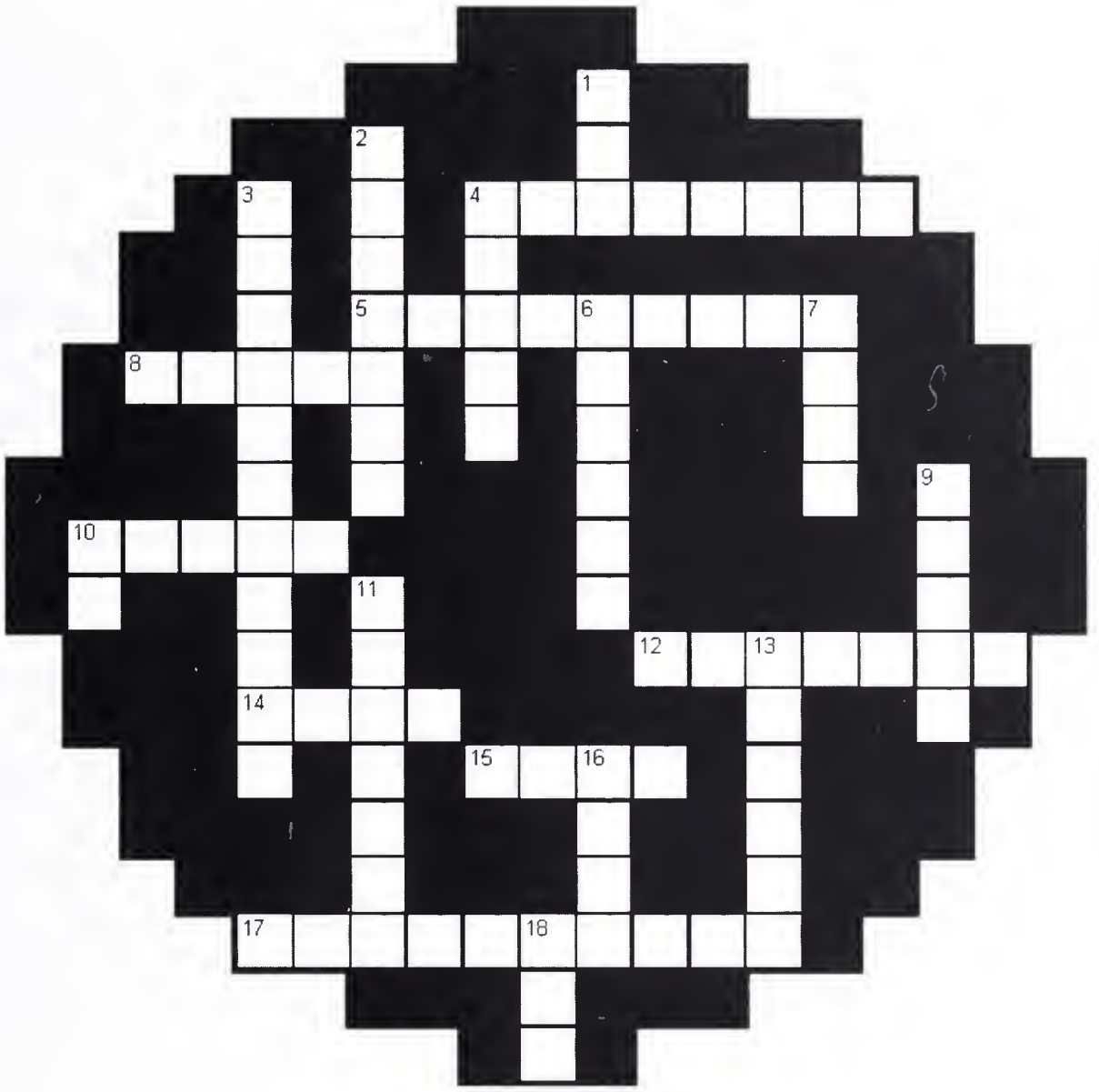
UTMJ Crossword (answers on page 225)

This month, the UTMJ would like to pay tribute to that lovely shape we've grown to love, the CIRCLE (not simply because it is the only template shape we have yet to use on our crossword software).

UTMJ salutes the CIRCLE

With the simplicity of its curvature and yet unattainable perfection, it certainly is a paradox to marvel. With our deepest respect, the crossword editors would like to hereby name the CIRCLE as the official geometric shape of the UTMJ. May we strive each day to live up to its excellence. You, too, can experience the paragon of the CIRCLE by trying the crossword below (remember it is UTMJ content oriented).



Across

4 Characteristic of Steve Singh's Clinician Profile (8)

5 Author P. Farmer links this to social inequality (9)

8 Lost down a drain in Canada (5)

10 Author S. Shem's acronym for "Get out of my emergency room" (5)

12 Seen in a conversation with Dr. T. David (7)

14 Is Vlad Miropolsky losing his ____? (4)

15 A market married to medicine (4)

17 Hypertension, smoking, atherosclerosis and atrial fibrillation leave one ____ (10) to stroke.

Down

1 This organization took the time to define Quality of Life (3)

2 Renaissance man involved in battle of the textbooks (7)

3 Nicholas Tan has a ____ ____ (11)

4 Descriptive of Pott's Tumor (5)

6 Acronym for primary burn care (6)

7 Descriptive of CIRCLE (4)

9 Utility measurements can be used to assess this (This clue is a doozie! Phew!) (5)

10 Abbrev. for the hormone excess of acromegaly (2)

11 UTMJ category of book review; broad interest (7)

13 A sepsis you don't want (6)

16 Circles make this editor sing (4)

18 Another current genome project (3)

In the Literature

Philippe L. Bedard, B.ArtsSc. (0T3)

This section of News and Views will present updates of recent advances in the medical and scientific literature.

Recombinant Human Activated Protein C reduces mortality from severe sepsis

In spite of advances in antibiotic development and supportive care, the rate of death from severe sepsis, is over 30 percent. Severe sepsis occurs when bacterial endotoxins trigger the widespread release of host inflammatory cytokines, such as TNF-α, IL-1ß, and IL-6, which activate coagulation pathways and produce diffuse endovascular damage leading to multi-organ failure and death. Activated protein C, an endogenous serine protease that promotes fibrinolysis and inhibits thrombosis and inflammation, is an important modulator of the procoagulant and inflammatory mechanisms in sepsis. Previous animal studies showed that administration of activated protein C improved outcome in baboons with *E. coli*-induced sepsis. In this multi-centre phase III clinical trial, 1,690 patients with sepsis and evidence of end-organ dysfunction were randomized to receive an intravenous infusion of either placebo (N=840) or recombinant human activated protein C (N=850). Exclusion criteria included a known hypercoagulable condition, a platelet count below 30,000, and HIV infection with a CD4 count below 50. Protein C infusion was associated with reductions in plasma d-dimer and IL-6 levels, indicating that the procoagulant and inflammatory effects of sepsis were diminished by treatment. Twenty-eight days after the start of the infusion, the mortality rate was 30.8 percent in the placebo group and 24.7 percent in the protein C group. The relative risk of death was reduced by nearly 20 percent in the treatment group. Protein C was effective regardless of age, severity of illness, the number of dysfunctional organs, the site of the initial infection, and the type of infecting organism. The only serious complication observed with protein C therapy was a slight increase in the risk of severe bleeding (3.5 percent in the treated group vs. 2.0 percent in the placebo group). In summary, the results of this trial demonstrate that treatment with human recombinant protein C significantly reduces mortality in patients with severe sepsis and is associated with a slight increase in the risk of severe bleeding.
(Bernhard GR, Vincent J-L, Laterre P-F, *et al.* 2001. *NEJM.* 344: 699-709.)

The role of chemokines in breast cancer metastasis

The main cause of treatment failure and death in cancer patients is metastasis, the spread of cancer cells beyond the site of the primary tumour. It has long been a mystery to researchers why different cancers are characterized by distinct patterns of tissue metastasis. For instance, breast cancer commonly spreads to the axillary lymph nodes, bone marrow, lung and liver, but rarely involves other organs. Chemokines are small, cytokine-like proteins that are involved in recruiting leukocytes and hematopoietic stem cells to particular anatomic sites. Through their interaction with G-protein coupled receptors on the surface of leukocytes and stem cells, cytokines trigger cytoskeletal rearrangement, adhesion to the endothelial cells lining blood vessels, and directional migration towards the chemokine source. Muller and colleagues hypothesized that tumour cells may use similar chemokine-mediated mechanisms during the process of metastasis. They compared the expression pattern of all known chemokine receptors in breast cancer cells and normal breast tissue, and found that the chemokine receptor CXCR4 was markedly upregulated in breast cancer cells. They showed that CXCL12, the chemokine agonist for the CXCR4 receptor, is constitutively expressed in many of the anatomic sites where breast cancer commonly spreads, such as lymph nodes, bone marrow, and lungs. By adding CXCL12 to breast cancer cells *in vitro,* they were able to stimulate breast cancer cells to carry out the basic steps in metastasis: actin polymerization, pseudopod formation, directional migration, and invasion through a reconstituted basement membrane. Using immunodeficient mice injected with human breast cancer cells, the authors then showed that metastasis to CXCL12-rich lung tissue could be blocked *in vivo* by adding a neutralizing antibody to CXCR4. These results demonstrate that chemokines and their receptors play a critical role in determining the metastatic distribution of breast cancer cells and raise the intriguing possibility that small-molecule antagonists of chemokine receptors may be useful in cancer treatment in the future.
(Muller, A, Homey B, Soto H, *et al.* 2001. *Nature.* 410: 50-56).

Using the Internet to deliver a behavioural weight loss program

Developing effective weight reduction programs is an important health promotion initiative, as over 54% of US adults are overweight or obese. Past research has demonstrated that even modest weight reductions of 5-10% of total body weight can improve obesity-related health conditions. Currently, group behavioural programs involving weekly clinic visits are the most effective treatments for obesity. However, their impact is limited, since most adults prefer to lose weight without having to participate in face-to-face treatment programs. With recent increases in public access to information technology, the Internet has become an increasingly popular mode of public health intervention. To determine how the Internet could most effectively be used to deliver weight reduction programs, Tate and colleagues randomly assigned 91 overweight adult hospital employees to a 6 month weight-loss program of either Internet education or Internet behaviour therapy. All participants were given one introductory group session and were provided with access to a Web site with links to weight loss resources. In addition, participants in the behaviour therapy group received 24 weekly behavioural lessons via e-mail, were given access to an online peer support bulletin board and were encouraged to submit weekly self-monitoring diaries online to receive

individualized therapist feedback via e-mail. Six months after starting the program, participants in the Internet behavioural therapy group showed greater weight loss (4.5kg vs. 1.6kg) and greater reduction in waist circumference (4.6cm vs. 2.3cm) than participants in the Internet education group. Moreover, a greater percentage of participants in the behavioural therapy group lost weight greater than or equal to 5% of their initial body weight when compared with those in the education group (45% vs 22%). Although the weight losses in the Internet behavioural therapy group were not as significant as those reported in previous studies with face-to-face behavioural programs, results of the study suggest that the structured Internet behavioural programs are a viable alternative for overweight adults unwilling to participate in face-to-face treatment programs.
(Tate DF, Wing RR, and Winnet RA. 2001. *JAMA.* 295: 1172-1177).

Successful Heart Transplantation in ABO-Incompatible Infants

Currently, heart transplantation is the only effective therapy for infants born with lethal congenital cardiac disease. Many infants with lethal cardiac disease die while awaiting transplantation because of the shortage of available donors. Traditionally, cardiac transplantation between donors and recipients with incompatible ABO-blood groups has not been performed because of the high risk of hyperacute rejection. Such rejection occurs when pre-existing serum anti-A and anti-B antibodies (isohemagglutinins) in the recipient bind to their respective blood-group antigens on vascular endothelial cells in the donor heart, triggering activation of the complement cascade and rapid thrombosis in the graft vasculature. Newborn infants are thought to be less susceptible to such ABO-incompatibility induced rejection because of the immaturity of their immune systems. Infants do not produce significant levels of isohemagglutinins until 14 months of age when their complement systems are less active. To determine whether ABO-incompatible cardiac transplantation is safe in young infants, West and colleagues studied 10 infants, aged 4 hours to 14 months, with lethal congenital cardiac disease who received transplants from donors with incompatible ABO-blood types. The only addition to standard cardiac transplantation protocol in this study was that plasma exchange to remove preformed antibodies was performed at the time of transplantation. Standard immunosuppressive therapy was given post-operatively and rejection was monitored during follow-up, which lasted from 11 months to 4.6 years, with endomyocardial biopsies. All 10 patients underwent successful transplants and no episodes of hyperacute rejection were observed. The overall survival rate was 80 percent, with 2 early deaths due to causes believed to be unrelated to ABO-incompatibility. No morbidity attributable to ABO-incompatibility was observed. Interestingly, only 2 of the surviving recipients developed antibodies against donor blood group antigens and no graft damage was observed histologically in these patients. After initiating ABO-incompatible cardiac transplants, the mortality rate among infants on the waiting list for transplantation declined from 58 to 7 percent. These findings indicate that ABO-incompatible cardiac transplantation is safe in young infants with lethal congenital cardiac disease and suggest that ABO-incompatible transplantation may be an effective means of reducing waiting list mortality.
(West LJ, Pollock-Barziv SM, Dipchand AI, *et al.* 2001. *NEJM.* 344: 793-800).

No difference between hyperbaric oxygen and slightly pressurized room air for children with cerebral palsy

Cerebral palsy (CP) is a collection of non-degenerative neurological disorders marked by abnormal motor function that arises from prenatal or perinatal injury to the developing brain. Hyperbaric oxygen has been widely used to treat children with CP, despite little scientific evidence of efficacy and reports of possible side effects, including middle ear trauma and convulsions. It has been theorized that hyperbaric oxygen may improve motor function in children with CP by increasing cerebral oxygenation. To evaluate the efficacy of hyperbaric oxygen therapy, 111 children with CP aged 3-12 years were randomly assigned to receive either 40 treatments of hyperbaric oxygen (N=57), which consisted of 100% O_2 at a pressure of 1.75 atmospheres, or slightly pressurized room air at pressure of 1.3 atmospheres (N=54). The primary outcome measure was gross motor function and secondary outcome measures included attention, working memory, speech and language, and activities of daily living. Participants in the study were evaluated using standardized tests at baseline, after 20 and after 40 treatments, and 3 months after the cessation of treatment. For all outcome measures, both groups improved equally over the course of the study and the improvements persisted 3 months after intervention. Gross motor function improved by 29% in children receiving hyperbaric oxygen and 30% in children receiving slightly pressurized room air. These results suggest that hyperbaric oxygen treatment does not improve the condition of children with CP when compared with pressurized room air.
(Collet J-P, Vanasse M, Marois P, *et al.* 2001. *Lancet.* 357: 582-86).

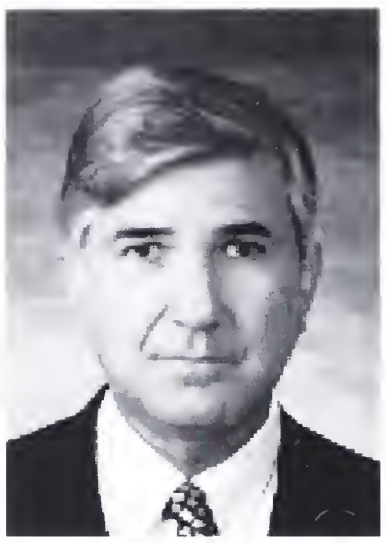
Moderate alcohol consumption may decrease systemic inflammation

Past epidemiological studies have demonstrated that consumers of moderate amounts of alcohol have lower all-cause mortality than non-drinkers and heavy drinkers, which is primarily related to a decreased risk of coronary heart disease. Although moderate alcohol consumption is known to induce favourable changes in lipoprotein and hemostatic profiles that are partially responsible for its cardioprotective effects, studies have shown that other mechanisms are also likely to be involved. There is increasing evidence that inflammation plays a crucial role in the initiation and progression of atherosclerosis. Locally, inflammatory cells, including macrophages and T cells, are prominent in the atherosclerotic plaque. Systemically, increased serum concentrations of C-reactive protein (CRP) and other acute phase inflammatory proteins are increased in patients with clinically apparent atherosclerotic disease. To investigate the relationship between alcohol consumption and systemic inflammation, Imhof and colleagues compared alcohol consumption, assessed by a self-reported 7 day food record, with serum markers of inflammation in a sample 2,006 adults aged 18-88 years. They found that male moderate drinkers had lower mean CRP, α1-globulins, α2-globulins, and leukocyte levels than male non-drinkers or heavy drinkers. This U-shaped relationship between alcohol consumption and serum markers of acute inflammation persisted after controlling for age, smoking, BMI, HDL and LDL cholesterol, history of hypertension, education, and income. In women, the U-shaped association between alcohol consumption and CRP and leukocyte levels was less strong, and concentrations of α1- and α2-globulins were inversely related to alcohol consumption. In summary, these findings suggest that moderate alcohol consumption may be associated with decreased systemic inflammation, especially in men, which may be linked to decreased cardiovascular and all-cause mortality.
(Imhof A, Froehlich M, Brenner H, *et al.* (2001). *Lancet.* 357: 763-66).

Prolific Clinician Profiles

A Conversation with Dr. Tirone David, M.D., F.R.C.S.(C.), F.A.C.S. Innovation, Passion & Cardiac Surgery

Steve K. Singh, B.Sc. (0T3)



Dr. Tirone David is a Professor of Surgery at the University of Toronto and Chief of Cardiac Surgery at the Toronto General Hospital. He was born in Brazil, where he graduated from medical school at the University of Parana in 1968. He undertook post-graduate training in cardiovascular and thoracic surgery at the State University of New York, the prestigious Cleveland Clinic and the University of Toronto. In 1978, he joined the academic staff of the University of Toronto and the Toronto Hospital.

Dr. David has become one of the leading cardiac surgeons in the world. Few equal his dexterity, speed and operative acumen. Hundreds of heart surgeons from around the globe visit his operating theatre every year. His patient-base is equally far-reaching; people from all around the world travel to Toronto specifically for Dr. David's help.

Dr. David has received international attention for his clinical research. In his prolific career, he has published over 150 peer-reviewed scientific papers, numerous chapters in textbooks, and four surgical textbooks. He has developed novel operative procedures to treat patients with heart valve disease, complications of myocardial infarction and thoracic aneurysms. He also developed the Toronto SPV™, a stentless porcine aortic valve.

Dr. David is a member of the editorial board of four cardiac surgical journals, the Secretary of the American Association for Thoracic Surgery and a member of numerous surgical and medical societies. He is an honourary member of the European Cardio-Thoracic Association and the Brazilian Cardiovascular Society. In 1993, Dr. David received the Order of Ontario and in 1997 he was appointed an Officer of the Order of Canada.

In April 2000, Dr. David was invited to speak at the American Association for Thoracic Surgery symposium for developing the aspiring academic surgeon. Considered the individual who has changed and advanced the field of cardiac surgery the most in the previous decade, he spoke to an international audience of residents and surgeons on the topic of innovation in surgery. Dr. David's numerous honours, accomplishments, and contributions are not only a direct result of genuine innovation, but also a consequence of an intense passion for what he does.

N&V: What attracted you to study Medicine and then specialize in heart surgery?

TD: Believe it or not, I wanted to be a missionary. I went to Africa for a while and worked with Dr. Albert Schweitzer. He was a German theologian and physician who developed a clinic in Equatorial Africa. I thought it was very noble. I went to medical school, but when I finished I realized that reality was much more complicated. I went to medical school a bit reluctantly. I majored in chemistry and I loved the financial opportunities, particularly back in the 1960s when the field of plastics and polymers was beginning. I thought this was where there would be endless opportunity. But deep inside I wanted something where I could relate to my fellow man without being a priest or a rabbi.

As I was in medical school, the first heart transplant was performed by Christian Barnaard from South Africa, and then truly developed by Dr. Norman Shumway from California. The intrigue with the heart increased. I guess that's how it started. By the time I finished medical school I had made up my mind that I wanted to be a heart surgeon. Heart surgery was just starting during that decade. I finished medical school in 1968, and by the time I moved to the United States to start my internship in 1970, heart surgery was not as established as it is now. It was a specialty with plenty of opportunities for an inquiring mind. That was the main reason for me.

Yet, to be quite honest, I enjoyed every aspect of medicine during medical school, except psychiatry and dermatology. Psychiatry, I almost failed. I loved nephrology. Majoring in chemistry, I knew a lot about body chemistry, electrolytes, fluids, pH, and why they affected cellular function. That stuff was fascinating. Endocrinology, neurology and neurosurgery were fantastic. But, I picked the heart and said, "that's what I want to do." One thing I knew was that because of my level of manual dexterity, I wanted to be a surgeon as opposed to an internist.

N&V: Your surgical skills are world-renowned. How did you

come to realize your abilities, and what do you attribute them to?

TD: In my summers during medieal sehool, I earned money by helping surgeons in Brazil. They told me that I had an unusual degree of dexterity. So I knew quite early in my youth to be quite honest. I loved to work with my fingers making airplanes out of balsa wood, but I don't think dexterity is a developed trait. I think it is genetically marked. Some of us are very dexterous. We seem to think in our training programs that we ean take a guy and make him a surgeon. We train them for five, six, maybe ten years, but we can tell by the second year who's going to be outstanding, who's going to be average, and who's going to fail.

N&V: As you mentioned earlier, it was an exciting time in the field of eardiae surgery when you decided to enter your specialty. There were many exciting characters like Drs. Cooley, Barnaard and Shumway. Were there any that you admired?

TD: It has always been an exciting time in cardiac surgery. This is because it is a speeialty that is eonstantly evolving. Yes, there were many characters at that time, but I didn't know any heart surgeons then. I grew up in Brazil and I had never seen heart surgery. When I eame to the United States, to be quite honest, my role model was a bowel surgeon, a man with tremendous insight. It was not what he taught me about intestinal disease and intestinal surgery, but it was his vision of surgery that made him ineredibly eaptivating. Then, my second role model was a head and neck surgeon. And yet, I end up being a heart surgeon. I don't think you have to have a role model in your specialty to become what they are in terms of what they have aecomplished and how they did so.

N&V: You are a very prolifie and aecomplished clinical researcher. Your interests include heart valve disease, aortie root aneurysms and mechanical complieations of myocardial infaretion. Could you comment on the state of advaneement of research in these areas and where your research fits in?

TD: Very early on in my eareer I started probing why we are the way we are. Why is my hand the shape it is? Why does it have five fingers and this range of motion? I realized that likely my hand is how it is beeause it represents the ideal shape to fulfill its function. In other words, form follows function. So during evolution, whatever has happened to the shape of our body is largely a consequence of the need for our function. If you take a look at the heart operations we do, many of them are totally absurd in that respeet. I believe that restoration of a normal form to fulfill a function is the way to do heart surgery. So instead of replaeing diseased heart valves, repair them. Instead of cutting the heart muscles if the heart muscle is dead, try to change the heart muscle to restore its original state.

In patients who had myoeardial infaretions, we used to go in and do infareteetomies and remove a portion of the heart. The mortality for this was sky-high. So we don't do infareteetomies any more. [But] why are they dying? Well, they are dying because the musele doesn't pump anymore. So why not support the musele with something [instead of removing tissue]? I apply this in every area. Nowadays, this has beeome not just a surgieal eulture, but also a whole area of research.

But if you go deeper and deeper you are going to realize that the form alters itself because of the eells, and these eells alter themselves because of their ehemieal composition. It becomes moleeular biology, which escapes my knowledge and goes into different domains. So in my entire career, I have stayed at the level that I understand. I looked at the whole organ and became an expert in researeh of the whole organ. People sueceeding me now, my residents, have to go to the next level and go deeper into the eells and moleeules to see why they beeame altered and try to reconstruct this to restore normal form. Likely, they are going to be more productive in the end.

N&V: Your innovation has been illustrated in your development of many surgieal proeedures. What are the David Procedures and how did they evolve?

TD: You don't go to bed, dream up a new operation and go in the operating room the next morning and do it. Innovation eomes from years and years of work. To innovate you have to know how something works in detail, and by having an incredible amount of knowledge you ean make it better. I started praeticing in 1979 and encountered many problems I eouldn't solve, and patients died. So I went back to books and read extensively. I also went baek to the lab and played with some hearts. That's how ideas came for potential solutions.

The first operation I invented was done out of desperation. No surgeon likes to lose a patient. I had done an operation that had gone very well, yet suddenly as we were elosing the ehest the heart tore apart [rupturing the posterior wall of the left ventricle]. From reading papers and textbooks, I knew that the operations described to solve this problem eame with a very high mortality, and 80-90% still died. There was no point in doing them on this poor old lady, so I eame up with the idea to approaeh the heart from inside and lay a pieee of perieardium all over the part that had torn. I published a case report. A month later, someone else came with a more difficult problem. In the same area of the heart [where the previous patient had ruptured] it was full of ealeium. Now, I couldn't suture a valve to ealeium because ealeium doesn't heal. I wanted to remove the ealeium, so I broke the heart *intentionally* this time. Like before, I sewed a pieee of perieardium from inside [to repair the tear] and then sewed the valve to that. The results were perfeet. So, reconstruction of the mitral annulus was the

first operation I invented. I was in practice for about 5 years at the time, and now it saves many lives. Then I applied the same process for a patient with an abscess in the heart. From there, I said, "it works for an abscess, works for spontaneous rupture, and works for calcium—why shouldn't it work for a heart attack?" I kept expanding the indications and the procedures got better and better.

In a similar fashion, I was trying to repair valves and came up with a new operation called the valve-sparing operation. Again, most of my operations are reconstructions of the whole organ. I don't have the skills or knowledge to go to a cellular level or deeper, so now we bring in basic scientists to go to the next level.

N&V: You have also developed the Toronto SPV™, a stentless porcine valve manufactured by St. Jude Medical. How did this come about and how did it improve on the alternatives, which are mechanical and stented tissue valves?

TD: The problem with heart valve surgery, particularly artificial valve surgery, is that our clinical experience far exceeds the knowledge of the interactions between the human body, the heart and the blood components. In other words, when you change the valve, you affect the blood, because the blood is in continual contact with the valve, and you alter the function of the heart. It is the interaction of these three parts that makes the operation a success or not. Pig valves in the 1980s, when I started, were obstructive. The blood flowing through them would lose energy, and they were not very durable. So I came up with the idea of removing the stent and tried them in pigs and sheep to see if they were better. That is how the stentless concept was born. If they are better or not, only time will tell. It takes 10–20 years to prove. My gut feeling is that it won't be any better as far as durability is concerned, as it is made of a non-viable tissue. But it opens the door for us to do new things. Now people are taking the stentless concept, removing all the antigenic material from pigs, and populating it with cells from the recipient. Others are working with genetic engineering to create a valve with the recipient's own tissue. So although it may not be better, it is an entirely new concept that opens the door to an incredible amount of new investigation. But the patients have been doing very well, and that's the important thing.

N&V: What advances in cardiac surgery do you see as the most promising and beneficial in the next five to ten years?

TD: Even in your professional lifetime, disease won't disappear. Will you see an abolition of disease because of manipulation of abnormal genes? I don't think it's going to happen very soon. If you look at the complexity of the genome, even though we now know the sequence, so what? The genomes of the fruit fly and human are more than 90% identical. This goes to show how little change is required to make a huge difference.

I still think surgeons will remain here for the foreseeable future. Whether we are going to do surgery the way we do it today depends on how other sciences develop along with medicine. Robotics in surgery, for instance, is enticing and attractive. Yet, although we have developed this robotic arm technology, we haven't changed the way we do an operation. A mitral valve repair, whether done by my hands or robotic arms, is the same procedure. We use the same stitch and the same suture. So is it necessary to know now that a robotic arm can do this? Instead, we have to develop techniques that are compatible to the robotic arm. To take a needle driver with a needle at the end, a suture at the end of the needle and sew the tissue like we sew with our own hands doesn't make any sense. It is time to develop newer techniques to treat the same disease that we now do open-chest. This, undoubtedly, is an exciting area for us to get better and better.

I'd like to probe further into the future, beyond 10 years. Maybe we will find ways to go inside the beating heart, or in the awake patient, doing what the cardiologists currently do in the cath lab. You have to develop things that are perhaps beyond my and your imagination. It cannot be the same technique as we do now. Things we do today, 10 years ago were unthinkable and 30 years ago — undreamable. That perhaps is the mission of man on earth — to continually get better.

N&V: You've trained all over the world, beginning in Brazil, then New York, the prestigious Cleveland Clinic, and now Toronto. Why did you choose to base your clinical practice in Toronto?

TD: Dr. Bill Bigelow was Chief of Cardiac Surgery at the Toronto General when I finished my training, and he made me an offer that was attractive. Plus, the opportunities to practice here were better than in the United States. When I finished my training in 1978, one of the pleasures of practicing in Canada was that when patients came to my office, we spoke about their disease and talked about their options. Money was never brought to the table. In the United States, if you didn't have insurance you could not have an operation. The hospital wouldn't allow me to bring you in. For a young academician who wanted to be a missionary, this was the aspect that attracted me to Canada. Don't get me wrong – I like money, and we all need money to live. But we make enough money as doctors in Canada. We don't become multi-millionaires able to buy buildings, airplanes and farms. However, if you like that you should be in business, not medicine.

N&V: What about the opportunities regarding funding for research?

TD: This is getting worse in Canada. However, we have always

found a way. Perhaps it is not necessarily the right way, but you can make alliances with industry. The richest entities are not the government. The richest entities are the private sector. If they think you are a promising investigator, they give money to you to do any research you like. That is how the Toronto valve was developed: companies paid me to develop it. The thing is, once you develop it, it is theirs, not yours, and you lose ownership. But again, if the primary reason was to make money, one shouldn't be in medicine in the first place.

N&V: Many of your patients travel from all over the world seeking your help to perform life-saving procedures that you have developed. How do you deal with this tremendous responsibility, compounded with the stress inherent to the critical nature of heart surgery?

TD: I was brought up in Brazil in a very religious home. Things tended to be exaggerated such that you'd burn in hell for this or that. You grow up full of guilt over anything you did wrong, and I don't think I've been able to divorce myself from this as yet. Every time I do something that ends up harming someone or something, the feelings of guilt are incredible. You don't sleep at night and it consumes you.

I happen to believe in God. I don't know if I believe in God the way that He was presented to me as I grew up. Human beings have the need to see, to feel, to measure our senses to understand nature and understand ourselves. I think God is above all this. God is the essence, the energy, what the universe is made of. Because you have intelligence, because you can change things and think rationally, I think you have a connection to God. I don't think I'm crazy, but I think I talk to God. I meditate, and although God does not talk to me all the time, He gives me enough strength to make rational decisions. This might be through my conscience or my brain. This is comforting to know—to know that you used the best possible judgment in making your decisions.

As well, at this stage of my life I am experienced enough to know what works and what doesn't work in heart surgery. So if somebody comes seeking help and I don't think I can help, I say no. I walk away. I'll spare myself the pain. Early in my career I was bolder. I could deal with much more emotional pain. As you get older you get more tolerant to physical pain, less tolerant to emotional pain. When I was younger I brushed death off. Now, I deal with it by meditation and reading.

But undoubtedly, my childhood in Brazil has affected my approach. I lived in a very small isolated town of about 4,000 persons. It was an interesting upbringing, very poor and very simple.

N&V: How else did your upbringing in Brazil affect your career?

TD: When I was 14, my father made me move to a larger city for high school, then medical school. During medical school, every assignment was from journals in English. I thought, "why am I learning this second hand? I should go to the source and get to know the guy who's the author. Why am I reading what he wrote? I should be writing with the author." That inspired me to come here and learn from the source. I tried for a while to go back to Brazil, but by then my level of my education and the level of the environment… we'll it's a decision we all have to make: stay here as an immigrant or go back and help your own. I don't regret that I chose to stay here. I never felt as an immigrant here. Canadians have been wonderful to me. My wife is American, my eldest child is American and I have two Canadian daughters. It is the United Nations everywhere in Canada, and that's wonderful that we can live this way.

N&V: Finally, what characteristics do you believe are essential to become a cardiac surgeon, and what advice would you give to an interested student?

TD: We all need passion to do a job well. It doesn't matter what you do, you have to have passion to be better than the average. I have a problem with average. I believe we should strive to be the best possible in our professions. [In] everything else you can be average. I've been a heart surgeon for 22 years and I'm still full of passion. I think that is what makes me strive to do better, to do research and try to find better answers to old and new problems. I can't imagine myself doing anything else but what I do now.

Each one of us is unique and different. I did as well as I have done because of a combination of multiple factors, particularly my dexterity and inquisitiveness. However, someone who has passion, is studious to keep abreast of new developments and is able to incorporate them into his/her practice, cares for their fellow man, and on top of that has common sense—he/she is a good surgeon and a very valuable member of the surgical team.

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The following page is dedicated to our hard-working *UTMJ* contributors and editors. The awards have been bestowed upon individuals who not only fulfilled their obligations to the *UTMJ* over the past year, but often went beyond their personal responsibilities, and were truly instrumental to the journal's success. Of course, many flattering adjectives could be used to describe the entire 2000-2001 *UTMJ* staff, but we did need to narrow down our choices to select individuals who were judged by the editors-in-chief and section editors to have made substantial contributions to the Journal. So, to our family of editors at the UTMJ, thank you for a truly memorable experience; it has been a pleasure to work with you.

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Law and Ethics in Medicine

When to Speak Out: The Dilemma for Medical Students

Anil J. Misir, B.Sc. (0T4)

Abstract

Medical students must often confront the issue of how to deal with impropriety on the part of teachers, be they staff members or residents. However, the student's unique position within the health care team presents a number of specific issues that must be considered and understood before the appropriate course of action can be taken. Though every case is different, an understanding of the general principles for dealing with impropriety is a first step in making the correct choices.

When asked to break unwritten social codes, medical students often find it difficult to confront superiors, be they staff physicians or residents, since their superiors not only have more clinical expertise, but they are also responsible for academically evaluating the student.

A student may choose to speak up in a variety of ways, ranging from simply talking to the resident or staff member to "whistle-blowing", which involves taking the matter to an external agency, such as a government body or the media, whether openly or anonymously. Though the extent of action may vary according to circumstance, the ethical and logical processes used to evaluate the course of action do not. A basic understanding of these issues is vital to making the best decision.

Clearly, the simplest approach for dealing with impropriety is to do nothing. Yet, this is a questionable choice. At the very least, it glosses over differences between cases. For example, maintaining silence about negligent care is quite different from not letting one's ideological beliefs interfere with care (e.g. not objecting on religious grounds to a colleague's recommendation that a patient undergo a therapeutic abortion). Nevertheless, it is clear that action entails risk: students may be mocked for asking questions or raising concerns; teachers and co-workers may consider them as rebels being disloyal to the team; they may be viewed as argumentative and unprofessional; or they may be considered a "snitch" in speaking to the offender's superior. Moreover, unlike staff physicians, nurses and other professionals, medical students may be graded by the very person they intend to report for inappropriate conduct. These factors are not trivial as they can directly hamper future career prospects and diminish the student's sense of self.

However, medical students are not fully trained doctors, who have legal responsibilities to report unethical or incompetent colleagues. Might medical students therefore have fewer obligations attendant with their fewer privileges? At the very least, students have the obligation to observe both good and bad practices, and the duty to attempt to incorporate those good practices into their medical practice. However, is this sufficient? The ethical basis of reporting a teacher comes from the moral imperative of "preventing serious foreseeable harm to others."[1] Students, as members of society, face this obligation. Yet, the ethical dilemmas that medical students encounter are rarely black-and-white. Often, the potential harm to the patient is not life threatening, whereas the risks of speaking up may be high.

In addressing this issue, it is necessary to define the role of the medical student. Critically, this depends upon the student's stage of learning and the specific setting. Students act as caregivers, researchers, observers, patient advocates and even as teachers themselves. Yet overriding all of these roles is the most important one: learning how to be a good physician. The primary role of the medical student is to acquire the knowledge and practical skills necessary to become a trained physician. It is not sufficient to learn solely by observation and by attending lectures. Medical students must also apply the skills they have been taught to become proficient physicians. Included among these skills is the matter of dealing with ethically ambiguous issues. It is far too late to learn this skill when one acquires the responsibilities of a practicing physician.

Regardless of the particular situation, four guiding principles should be universally applicable in dealing with impropriety. Students must consider (1) the character and certainty of their conclusion, (2) their role in the clinical setting, (3) the possibility of harm to the patient, and (4) both the efficacy and potential personal cost of speaking up.

Students may question their judgment for at least two reasons. First, students have less clinical expertise than their teachers, and therefore, may underestimate their ability to fully appreciate the medical practices and issues involved. Indeed, as the most inexperienced member of the health care team, students may doubt their own ethical understanding of the issue.[2] However, neither situation should be a reason for remaining silent, since medical ethics generally involve some degree of uncertainty.

Second, the duties of the student in a given setting are an important factor in decision making. When actively involved in long-term patient care, students have a greater obligation to speak up given the more involved role of the student. However, there may be situations where a student with only a peripheral relationship to a patient should voice his concerns.[5] A case where a student on the wards notices obvious incompetence on the part of the resident or staff member might be one such example.

Third, it is essential to consider the potential impact of the impropriety to the patient. In cases of grave threat to a patient's health, students should speak up regardless of their uncertainty or position. If the risk to the patient due to inaction by the student is less obvious, however, the decision to question a superior becomes more difficult.[5]

Finally, the *effectiveness* of speaking up should be considered against the cost to oneself. If reporting a superior will have little effect, there is little benefit in speaking out. However, this must not be an excuse to constantly rationalize against action. Voicing one's concerns quite often makes a difference and doubts in this regard should not be exaggerated. At the same time, students can legitimately consider costs to themselves. Forfeiting one's career for a trivial matter is not necessary, but keeping quiet on a significant matter merely because it *may* have an impact on grades or career is equally misguided. Obligations, by definition, often incur a cost or inconvenience. Medical students frequently keep silent in the belief that speaking up will cause them to get a lower grade than they deserve, thus decreasing their chances of getting into the residency of their choice. When this becomes a real possibility, medical students may have to decide between maximizing their marks or satisfying their moral obligations. Perhaps it might be beneficial to examine the notion of a "good residency". Is the residency a good one merely because of prestige, or it is a good training program for future physicians? If it is the latter, then medical students must realize the irony of choosing not to act as conscientious physicians now, so they can pursue a residency where they will subsequently learn to become conscientious physicians.[5]

Just as important as the decision about whether one should take action is the notion of *how* one should take action. If the student decides to speak to the person involved, there is still the issue of how to express concern, as it is more than a simple matter of style and elocution. This is important, since many of the problems that students may encounter need to be resolved face-to-face. Few problems can be resolved by other methods such as anonymous letters or emails, though these certainly have their place; if a student, despite his best efforts, still finds himself uncomfortable with speaking to the offending party, these may be options to consider. Internal channels may provide hesitant students the opportunity to discuss their concerns openly while at the same time providing support and clarification in a non-judgmental manner. For example, the Office of the Dean of Student Affairs at the University of Toronto includes this function within its mandate.

Nevertheless, face-to-face interaction is arguably the best way for concerned students to voice their concerns in such a way as not to alienate fellow co-workers. This may take practice, perhaps as much as other medical skills. This skill, however, is vitally important, since the vast majority of students will be faced with a moral dilemma over the course of their studies. A recent study found that 35% of first year students in an American medical school observed unethical behavior by a superior. That number rose to 90% among fourth year students.[6] Thus, for medical students, the decision to report or confront a teacher is a difficult one, but one that will be faced. It is something, which must be carefully considered, without hasty action or undue fatalism. In any case, students must appreciate that there is a continuum of choice and action. Though decisions are often difficult, the choice is easier if all factors are understood.

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Forum

Exploring the Use of Physician Report Cards

Christopher J. Hall (0T3)
Ann M. Stewart, M.Sc. (0T4)

Forum
Introduced to the UTMJ for the first time earlier this year, Forum is a section that presents varying viewpoints on issues which have sparked debate within the medical community. In the introduction that follows, some of the facts surrounding the issue of physician report cards are briefly presented in order to provide some background information. Two different perspectives on this topic are then presented, one from Dr. Jack Tu and Dr. Curry Grant of the Institute for Clinical Evaluative Sciences, and one from Dr. Allan Detsky, Professor of Health Administration and Medicine at the University of Toronto. The ultimate aim of this article is to broaden the reader's understanding of the issues regarding physician report cards, and to stimulate further discussion about the effectiveness of their use.

An Introduction to Physician Report Cards

Ann M. Stewart, 0T4

Consumer guides to the health care system are widely available in the United States. Those providing specific information and statistics describing the performance of physicians include: *Best Doctors in America, How to Choose the Top Doctors, The Consumer Guide to Coronary Artery Bypass Graft Surgery* and the *New York State Coronary Artery Bypass Surgery Report*.[1,2,3] The guides are popular with patients because they allow consumers the chance to 'shop around' for what appears to be the best medical care. When people face frightening medical conditions that require significant medical or surgical intervention, they may feel intimidated by the system; thus, it is not surprising that they seek out advice on how and where to get the best care. It is also not surprising that doctors have mixed feelings about these reports, since statistics on mortality rates might not necessarily be an accurate reflection of their talents as physicians. Canadian physicians also worry that physician report cards might promote a sort of competition for low-risk patients, which may be detrimental to the future of publicly-funded health care in this country.

Physician report cards became publicly available in the United States in the early 1990's when a *Long Island Newsday* reporter attempted to uncover statistics concerning the performance of individual cardiac surgeons. The reporter knew that the New York State Department of Health had compiled a database of this information, but had no intention of releasing it to the public. Instead, after discovering large discrepancies between the performance of surgeons, the state had planned to send the relevant data directly to the hospitals in an attempt to improve their quality of care. Upon deciding that this information was far too important to remain concealed from the public, the newspaper filed suit against the state and won a landmark decision. In the judgment, the Supreme Court of New York State ruled that the state had a duty to release the information, as it was in the public's best interests to have free access to this data. *Newsday* then published every surgeon's mortality rates as a kind of scorecard.[4] Since then, the New York State Department of Health has published the *Coronary Artery Bypass Surgery Report* every year (http://www.health.state.ny.us/home/html, search "coronary bypass"). It is interesting to note that mortality rates for Coronary Artery Bypass Graft (CABG) surgery in New York State have declined in nine of the ten years since the report has been published.[5] Other states have joined New York in releasing individual physician statistics, including Pennsylvania with its *Consumer Guide to Coronary Artery Bypass Graft Surgery*. (http://www.phc4.org/reports/cardiaccare.htm).

Physician report cards on CABG surgery typically include statistics on the number of operations performed by the surgeon, and the actual patient mortality rate. This number is then compared to a risk-adjusted rate, which estimates the expected patient mortality rate. This is an attempt to statistically compensate for the higher mortality rates observed among physicians treating patients with poorer prognoses. Thus, a physician who treats very sick patients would theoretically not be penalized in the state rankings by receiving a high mortality rate score, as their risk-adjusted expected mortality would also be high.[6] After completing these statistical adjustments, physicians are individually ranked in reports which identify them by name, as well as by the hospital that employs them. The most established report cards available for individual physicians are for cardiac surgeons, but hospital report cards that outline success rates in other areas of medicine, such as obstetrics, have also been produced in a number of states (http://www.healthscope.org). In addition, some U.S. states, including Massachusetts, provide toll-free numbers where the public can find out whether or not a doc-

tor has been found negligent in a malpractice suit or convicted of a criminal offence.[7] Though some guides are published by business-people or patient advocate groups, and may be based on information collected through surveys of doctors and patients, most are produced by state health authorities or 'arms-length' independent state-funded organizations, using statistics gathered by the state.

The public demand for accountability in the medical profession has become greater in recent years, prompting politicians at both federal and provincial levels of government to address the issue of evaluating our health care system.[8,11] Though statistics on the performance of individual physicians are not yet being compiled in Canada, there are currently several agencies in the province of Ontario which provide statistics concerning the health care system as a whole. For example, the Institute for Clinical Evaluative Sciences (ICES), has published a hospital report card focusing on cardiac care, entitled *Cardiovascular Health and Services in Ontario: an ICES Atlas*, (http://www.ices.on.ca).[9] The atlas reports on both clinical outcomes (such as mortality rates) and process of care measures (such as rates of drug prescription). The Ontario Hospital Association and the University of Toronto have also published hospital rankings (http://www.oha.com).[10] They rate hospitals across Ontario as above or below average in a variety of areas, including clinical outcomes (for conditions ranging from acute myocardial infarction to asthma) as well as financial viability and patient satisfaction.

Many issues surround the publication of individual physician report cards. The medical profession should be accountable to the people it serves, but caution is warranted to avoid misleading the public with statistics which may not accurately represent a physician's capabilities. The effects that report cards have had on health care in the United States seem to suggest that they might prove to be a useful method of improving the standard of medical care in Canada, but careful planning is needed to avoid the pitfalls of inappropriate use of the information they provide. Clearly, arguments can easily be made both for and against physician evaluation. We now leave it to Drs. Tu, Grant, and Detsky to further illustrate these arguments both for and against the implementation of report cards.

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Is the Time Right for Physician Report Cards?

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There is increasing demand from government payers and health-care consumers for accountability within the medical profession. From the government perspective, provision of high-quality care at a reasonable cost is paramount. The consumer requires timely access to competent and caring physicians' services. The physician has a professional obligation to provide these services, and to maintain competence in an era of rapid changes in patient care and practice environments. For these reasons, physician report cards are potentially appealing to all three levels: payer, consumer and provider. For payers and consumers, physicians would be more accountable for the quality and the costs of care. Physicians, meanwhile, would receive valuable feedback on performance and comparisons with peer groups. This would allow them to make specific changes in their practices, and to improve their knowledge and skills. The reports would complement the ongoing efforts in maintenance of competence by professional societies by highlighting areas of improvement for individuals and specialty groups. There may be a reduction in adverse outcomes leading to malpractice suits if deficiencies are detected and corrected. Costs may be reduced by better adherence to clinical practice guidelines. For example, use of diagnostic tests and prescription of medications may be improved. Feedback on preventive health practices such as vaccinations and screening mammography has the potential to improve public health and reduce long-term costs.

While the concept of report cards is appealing, there are several practical difficulties in their use. Individual physicians may treat only small numbers of patients with a particular condition such as diabetes, making it difficult to distinguish adverse outcomes due to poor practices from those caused by the play of chance. Because of the differences in illness severity in patients among different medical practices and hospitals, a statistical risk-adjustment model must be used. Some physicians might resort to "gaming" to ensure better outcomes. For instance, they may either refuse to treat high-risk patients such as the elderly, or transfer these patients to other physicians. It would be difficult to define appropriate indicators applicable to a broad range of physician specialties, and specialty-specific indicators would be necessary. This would give rise to problems in weighing the importance of indicators. For example, should a high operative mortality rate for a surgeon be considered more important than a family physician's failure to employ appropriate screening mammography? If the reports were made public, some physicians might unjustly suffer economic losses as patients migrate to physicians with apparently better reports. Poorly performing hospital physicians and surgeons may face loss of hospital privileges or cancellation of contracts.

So far, there has been limited experience with physician report cards or "profiling" for specific conditions. New York State's Cardiac Surgery Reporting System was the first reporting system to employ detailed clinical information to develop credible comparisons outcomes of hospitals and cardiac surgeons. There were

limitations of the reporting system pointed out by Green and Winfield.[1] The risk adjustment model had moderate ability to predict mortality rates for surgeons and hospitals, while the quality of the data was also questioned since there may have been extensive "upcoding" of patient risk factors to lower the risk-adjusted mortality rates. Critics have charged that surgeons were avoiding "high risk" patients, in order to lower their mortality rates.[2] However, a careful analysis showed that surgeons' acceptance of high risk patients did not appear to bias their risk-adjusted mortality rates.[3] Despite the stated limitations of the Cardiac Surgery Reporting System, however, there is evidence that the system has had positive effects on the quality of cardiac surgery in New York State. For instance, there was a decline in the coronary artery bypass risk-adjusted mortality rates after the introduction of report cards while several low-volume surgeons with high mortality rates emigrated from the state after their publication. The report card results also stimulated one hospital to analyse its processes of care and to make changes to improve outcomes.[4] Processes of care for critically ill patients were improved, reporting of patient risk factors was more complete, and a collaborative atmosphere among specialists was established. Hospitals with lower mortality rates experienced greater growth in market share and surgeons had increased charges compared with those having higher mortality rates,[5] suggesting that report cards may incur economic benefits for hospitals and physicians with good results. A potential downfall of report cards is that the results may be ignored or misinterpreted. Although most health maintenance organizations emphasized the quality of cardiac surgeons in their hiring practices, only 20% indicated that the report cards were a major factor in their hiring decisions.[6] The Pennsylvania *Consumer Guide to Coronary Artery Bypass Surgery* was widely read by cardiologists and surgeons, but it had little impact on their practices.[7] Problems identified included the use of mortality as the only risk indicator, inadequate risk adjustment, and lack of reliability of the data. The need for increased collaboration involving physicians was identified.

Because of increasing demands for physician accountability from payers and consumers, the question is not *whether* to implement physician report cards, but *how* and *when* to implement them.[8] We believe that there are a number of very important methodological issues that need to be resolved satisfactorily before any information about physicians is made public. More research needs to be done on risk-adjustment methods.[9-11] Appropriate process and outcome measures should be selected to ensure adequate sample sizes that allow valid statistical comparisons to be made. Expert panels should set professional standards for outcomes. Comparisons should be based on precisely defined, objective clinical variables to avoid "gaming". Many of these issues could potentially be resolved through a partnership involving physicians, professional organizations, researchers, and patients. The medical profession in Canada should demonstrate leadership on this important issue rather than waiting for the government or other third-parties to develop physician report cards with no or minimal physician input, as has occurred in the United States.

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Physician Report Cards: Can the dissemination of information ever do harm?

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When I was a medical student (1974-78), the school I attended published and disseminated the student evaluations of every preclinical course and clinical rotation. Every student could comb through the series of statistics summarizing the numerical scores given for specific attributes of each course (objectives clearly described, written material adequate, teachers knowledgeable and approachable, etc.), as well as read the text of actual comments made about the courses and our professors. At the time, I believed that the publication of these statistics and comments had a great deal to do with motivating our teachers to do a good job and continuously improve. None of them wished to be publicly embarrassed by bad ratings.

F. Curry Grant and Jack Tu have succinctly and eloquently argued that payors and health care consumers would greatly benefit from a similar reporting mechanism on the quality of care provided by individual physicians. As well, they note the experience in the United States of institutional report cards and their effect on improving overall quality of care.[1] I concur with their belief that accurate and meaningful information would be extremely useful for consumers in making informed choices about where they should receive care and for payors in holding practitioners and institutions accountable for the reimbursement they receive. However, is it possible that this information may do more harm than good?[2]

In order to begin answering this question, we must consider two of the enormous difficulties in looking at individual physician report cards based on outcomes (e.g., surgical mortality rates): small sample sizes and inability to adjust for severity of illness. When individual doctors or institutions are confronted with worse than average statistics on outcomes, or even efficiency measures such as length of stay, the most common response they give is, "our patients are older and sicker". Statistical modeling to adjust for severity is difficult and does not always do the job; thus, at the level of individual physicians where sample sizes are relatively small, modeling is almost certain to be inadequate.

The issue of small sample sizes for each individual practitioner also leads to wide confidence intervals around estimated variables such as mortality rates and noticeable instability. The rank order of outcomes across hospitals commonly varies greatly from year to year because of the instability of these estimates.[3] For individual practitioners, this problem would be much worse.[4] (Remember what mutual fund companies tell all prospective clients: past performance is not necessarily an indication of future performance!)

Another problem, which is commonly referred to as "gaming", relates to individual physician behaviour that might occur as a result of report cards on outcomes and length-of-stay. Imagine that you are a surgeon whose individual mortality rates are reported to your colleagues, hospital administrators, and the public. Imagine also that you have excess demand for your services and can choose your patients based on your own preferences. It is almost certain that you will "game" the system by choosing to operate first on those patients who you believe are most likely to have the lowest chance of the measured adverse outcomes or the shortest length of stay. As time goes by, your statistics look better than your colleagues' and demand for your services goes up. This further enhances your ability to "cherry pick" and eventually you have the best statistics and your colleagues' statistics worsen.

In some institutions, surgeons are assigned to cover specific time periods for operating on patients, e.g. one week at a time. If the surgeon knows that a bad outcome occurring in a patient assigned in this manner will be attributed to him or her, there will be an incentive to delay the procedure to the next week thereby avoiding this potential blemish on his or her record.

The extent to which this information is used to evaluate an individual clinician's performance will determine how much gaming is attempted. If the stakes are very high, one could expect a lot of this kind of behaviour. Though this phenomenon might prove to be beneficial in that the patients who are most likely to receive the interventions are those who are at lowest risk, it would be unfair to exclude or discriminate against patients who are more severely ill simply because practitioners wished to receive better grades.

In the hands of those who wish to use outcome measurements to improve overall quality of care, such as the Northern New England Cardiovascular Group,[1] outcome data was shared among practitioners but not made public. The practitioners then learned from each other and outcomes were improved across all institutions. Such a venture requires cooperation which may be difficult to obtain if practitioners believe that misleading data will be immediately reported to the public.[5] Finally, one must not ignore the substantial cost associated with collecting accurate outcomes data.

In my opinion, it is too early to use individual physician based outcome report cards to make informed decisions and the widespread publication of this information will likely do more harm than good. On the other hand, process based report cards (e.g., what proportion of a primary care practitioner's patients are immunized, screened for cervical cancer, treated with beta-blockers post-myocardial infarction, etc.) are much less likely to have these kinds of difficulties.

Report cards are a good thing. However, the data presented must be meaningful in order for them to be useful in improving outcomes.

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Evidence-Based Medicine:

The Canadian Task Force Periodic Health Examination

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Abstract

The periodic health examination plays an important role in both primary and secondary prevention practices in Canada. The recommendations that support the inclusion or exclusion of various preventive maneuvers are based on the evidence in the scientific literature. This paper will introduce the process of evaluating the evidence and setting the recommendations. Several cases will also be presented to illustrate the key concepts and to demonstrate some of the difficulties that arise when trying to incorporate these maneuvers into daily practice.

Introduction

The Canadian Task Force on the Periodic Health Examination was established by the Deputy Ministers of Health of Canada in 1976.[1] Its purpose was to evaluate the effectiveness of specific maneuvers and to institute guidelines for the periodic health assessment. The original Task Force report was published in 1979 and it reviewed the evidence for 78 conditions. Since that time, there have been nine updates, which have expanded the coverage to over 200 conditions, and which have also revised previous recommendations as new evidence emerged.

The Task Force described the following criteria to select the health conditions that were to be assessed:[1]

1. the burden of morbidity and mortality of the condition;
2. the performance characteristics of early detection procedures (i.e. acceptability);
3. the effectiveness of preventive interventions.

The evaluation of the evidence and the recommendations for these conditions can be found in the Canadian Guide to Clinical Preventive Health Care.[2] The online version of this guide can be found at:
http://www.hc-sc.gc.ca/hppb/healthcare/pubs/clinical_preventive/index.html

Evaluating the Evidence

Once the health conditions that require assessment are identified, the evidence for specific maneuvers associated with these conditions must be evaluated. The first step involves a standardized approach to searching the literature to ensure that all relevant studies pertaining to this condition are collected. The next step involves separating those studies that present epidemiologic evidence of associations (studies showing that persons with a modifiable condition identified through screening are at increased risk for disease) and those that are intervention studies (studies showing that persons receiving the maneuver have better outcomes compared to controls).[3] In general, the Task Force has made this distinction in order to focus their reviews on studies that involve clinical interventions. After this distinction is made, the quality of the individual studies needs to be judged. This rating is based on a five-grade classification system that favours study designs such as double-blinded, randomized, controlled trials, which have less bias and greater validity (Table 1).[1]

Table 1
Task Force Classification of Study Designs[1]

I:	Evidence obtained from at least one properly randomized control trial
II-1:	Evidence obtained from well-designed controlled trials without randomization
II-2:	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
II-3:	Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments
III:	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Once the design category has been classified, the individual studies are critically appraised to assess design strengths and flaws. The actual process of critical appraisal is discussed elsewhere[4-6] and is beyond the scope of this paper. It should be noted, however, that every effort is made to ensure that each maneuver is assessed using the same set of criteria, thereby

improving the consistency with which the evidence is evaluated. Some of the criteria used to critically appraise the studies are included in Table 2.

Table 2
Criteria for Critical Appraisal[3]

- Presence of blinding
- Treatment of confounders
- Statistical power
- Clear specification of hypothesis (prior to any inspection of results)
- Primary endpoints
- Data analysis methods
- Consideration of potential sources of bias
- Post hoc data analysis
- Proportions of persons lost to follow up

Finally, the results of the assessment, including the strengths and the weaknesses of the various studies, need to be reported in an organized, comprehensive manner.[3] Key elements of the studies that should be included are the sample size as well as the direction, magnitude and statistical significance of the outcomes.[7] The rationale for judging the quality of the evidence is carefully documented in a logical fashion, allowing readers to make their own assessments.

Developing the Recommendations

The Task Force wanted to present the recommendations in a way that would be practical for the physician in general practice to follow. As a result, it created recommendations in a "do it" or "don't do it" format.[2] Upon review, the scientific evidence did not lend itself to be outlined in such a simplistic manner, and a bi-directional graded scale was subsequently established (Table 3) that equates strength of recommendation with the quality of the evidence.[1]

Table 3
Classification of Recommendations, by Grade

A	Good evidence to support inclusion in the periodic health examination (PHE)
B	Fair evidence to support inclusion in the PHE
C	Poor evidence to support inclusion or exclusion in the PHE
D	Fair evidence to support exclusion from the PHE
E	Good evidence to support exclusion from the PHE

As a rule of thumb, an *A* recommendation is given to any maneuver that has type I evidence (properly randomized, controlled trial) supporting its inclusion. A *B* recommendation is given to any maneuver that has type II evidence (controlled trial without randomization, case-control, or cohort studies) supporting its inclusion. A *C* recommendation is given to any maneuver that has no evidence for or against inclusion. A *D* recommendation is given to any maneuver that has type II evidence supporting its exclusion. An *E* recommendation is given to any maneuver that has type I evidence supporting its exclusion. Although the type of study and quality of evidence are important in deciding whether to include or exclude maneuvers in the periodic health examination, they are not the only factors that contribute to the development of the clinical practice recommendations. A list of other factors that are considered before making a recommendation is included in Table 4.[3]

Table 4
Factors to Consider when Making Recommendations

- Type of outcome measure used in the study
- Generalizability of study results
- Patient compliance/acceptance of maneuver
- Issues surrounding insufficient evidence
- Risk of the condition if left untreated
- Prevalence of the condition in the population
- Cost considerations (if data about cost exists)

Since the process of recommending a maneuver is complex, the rationale for arriving at the final recommendations must be well documented. This provides important information that will help clinicians to make sound decisions about the implementation of a maneuver in their everyday practice. This also allows for individual assessment of the issues surrounding any given recommendation.

Exercises

The following cases serve several purposes. First, they offer an opportunity for the reader to identify how closely his or her personal convictions about a specific maneuver align with the Task Force recommendations. Therefore, readers are encouraged to guess what the Task Force recommendation would be while reading the cases, before checking the answers. Second, the cases will serve to illustrate the rationale behind the setting of recommendations and the evaluation of evidence. By using specific examples, these cases will reinforce some of the important principles surrounding the process of assessing preventive maneuvers. Finally, the cases have been selected to demonstrate some of the difficulties that arise when trying to implement these recommendations in clinical practice.

CASE # 1

A 55-YEAR-OLD MAN IS AT YOUR OFFICE FOR HIS YEARLY CHECK UP. HIS FATHER DIED 5 YEARS AGO FROM LUNG CANCER. HE IS CONCERNED ABOUT WHETHER HE WILL DEVELOP LUNG CANCER IN THE FUTURE, AND INQUIRES ABOUT A SPUTUM CYTOLOGY TEST TO SCREEN FOR LUNG CANCER. WHAT DO YOU TELL HIM?

CASE # 2

A 53-YEAR-OLD WOMAN COMES TO YOUR OFFICE AND INQUIRES ABOUT MAMMOGRAPHY SCREENING FOR BREAST CANCER. WHAT DO YOU TELL HER?

CASE # 3

A 21-YEAR-OLD FEMALE UNIVERSITY STUDENT ATTENDS THE STUDENT HEALTH CENTRE INQUIRING ABOUT ORAL CONTRACEPTIVES. UPON TAKING A SEXUAL HISTORY, YOU DISCOVER THAT THE PATIENT HAS NEVER HAD A PAP SMEAR. WITH HOW MUCH CONFIDENCE DO YOU RECOMMEND A PAP SMEAR?

CASE # 4

A 58-YEAR-OLD MAN SAYS THAT ALL OF HIS FRIENDS HAVE HAD A PSA TEST DONE. HE IS CONVINCED THAT THE TEST IS NECESSARY AND USEFUL TO MAKE SURE THAT HE HAS A HEALTHY PROSTATE. WHAT WOULD YOU TELL HIM, AND WHAT WOULD YOU DO?

CASE # 5

A 53-YEAR-OLD MALE WAS WATCHING TELEVISION AND HEARD ABOUT COLONOSCOPY SCREENING ON A DAYTIME TALK SHOW. HE WANTS TO BE SCREENED FOR COLON CANCER DESPITE A NEGATIVE FAMILY HISTORY FOR COLON CANCER. WOULD YOU CONSIDER THIS MAN FOR SCREENING BY COLONOSCOPY?

ANSWERS TO THE CASES

CASE # 1
SPUTUM CYTOLOGY SCREENING FOR LUNG CANCER

LEVEL OF EVIDENCE

There have been two large randomized, controlled trials that have evaluated the effectiveness of screening by sputum cytology in reducing the rate of death from lung cancer.[8,9]

WHAT THE EVIDENCE SHOWS

Both of these trials showed that there was no significant difference between either the detection rate of lung cancer or the mortality rate between the intervention and control groups.[8,9]

TASK FORCE RECOMMENDATION: **E**

Based on level I evidence (randomized, controlled trials) indicating that sputum cytology is an ineffective method for detecting lung cancer and for reducing mortality due to lung cancer, there is good evidence to exclude this maneuver from the periodic health examination.

CASE # 2
MAMMOGRAPHY SCREENING FOR WOMEN AGED 50 TO 69

LEVEL OF EVIDENCE

There are four randomized, controlled trials that examine the benefits of mammography alone for breast cancer screening.[10]

WHAT THE EVIDENCE SHOWS

All of the studies show a significant reduction in mortality in women aged 50 to 69 after undergoing mammography screening.[10]

TASK FORCE RECOMMENDATION: **A**

Based on level I evidence (randomized controlled trials) demonstrating the ability of mammography screening to significantly reduce mortality in women aged 50 to 69, there is good evidence to include this maneuver in the periodic health examination for women aged 50 to 69.

KEY POINTS

The first two cases illustrate the emphasis that is placed on randomized, controlled trials with mortality as the outcome measure by the Task Force. When a randomized, controlled trial shows a significant reduction in mortality, there is a strong recommendation to include the maneuver in the Periodic Health Examination. Conversely, when a randomized, control trial shows no difference in mortality, there is strong evidence to exclude the maneuver.

CASE # 3
PAPANICOLAOU (PAP) SMEAR TEST FOR CERVICAL CANCER SCREENING

LEVEL OF EVIDENCE

Since the Papanicolaou (Pap) smear test has been widely available for cervical cancer screening, it would be unethical to assess the benefit of the Pap smear test by ways of a randomized controlled trial. Therefore, the evidence that exists comes from cohort and case-control studies.[11,12]

WHAT THE EVIDENCE SHOWS

All of the cohort and case-control studies show a reduced incidence of invasive disease as a result of participation in cervical cytology screening programs.[11,12]

TASK FORCE RECOMMENDATION: **B**

Since the highest level of evidence supporting a reduction in the incidence of invasive disease is level II-2 (case-control and cohort studies) evidence, there is only fair evidence to include this maneuver in the periodic health examination.

KEY POINTS

This third case demonstrates the importance of understanding the definition of the various recommendation levels. Pap smear testing is an invaluable screening tool that has been extremely effective in reducing the incidence of cervical cancer due to the effective management that exists for lesions that have been detected early. The *B* recommendation that Pap smear screen-

ing receives reflects the level of evidence that exists, but should not be the sole measure that influences its use in clinical practice. One thing to keep in mind whenever one is considering a *B* recommendation is to determine whether it is ethical to conduct randomized, controlled trials to study the benefits of that maneuver. If it is unethical to do so, as in the case of Pap smear testing, an *A* recommendation by definition is rarely possible.

CASE # 4
PSA SCREENING FOR PROSTATE CANCER

LEVEL OF EVIDENCE

There are cohort analytic (descriptive) studies for prostate-specific antigen (PSA) screening.[13-16] No randomized, controlled trials have been performed to date to assess the effect of PSA screening on prostate cancer and all-cause mortality.

WHAT THE EVIDENCE SHOWS

The descriptive studies report sensitivity values ranging from 72% to 90% and specificity values ranging from 59% to 90% for the ability of the PSA test (over 4 ng/mL is considered a positive test) to identify patients with prostate cancer.[17] The positive predictive value of the PSA test ranges from 14% to 35%, depending on the study.[17] Most men who test positive will undergo a prostate biopsy.

TASK FORCE RECOMMENDATION: **D**

When prostate cancer prevention was most recently reviewed by the Task Force in 1994, there were only studies with level II-3 (cohort analytic-descriptive studies) evidence for the use of prostate-specific antigen (PSA) screening. Not only do these studies have a low grade based on the Task Force classification system, they were all deemed to have methodologic study design problems.[18]

The Task Force's rationale behind the recommendation for PSA screening can be summarized in several key points. First, all studies showed that the PSA test has a low positive predictive value (only as high as 35%), so many patients with a positive test will undergo unnecessary follow-up procedures such as prostate biopsies. Second, there is no compelling evidence that early detection of prostate cancer by PSA screening will improve outcome. Many people will die with prostate cancer, rather than from prostate cancer, which begs the question: "Does early detection of prostate cancer do more good than harm?" Finally, PSA testing is not very sensitive in detecting occult cancers (approximately 80% sensitivity), which means that 20% of men with cancer that are screened will have a false negative test.

Due to these poor test characteristics, the lack of evidence surrounding outcome, and the potential harm of unnecessary follow-up, the Task Force could not recommend this test, stating that there is fair evidence to exclude this maneuver from the periodic health examination.

KEY POINTS

This case demonstrates the amount of uncertainty that can surround a Canadian Task Force recommendation. Many questions remain unanswered in the PSA screening debate. Evidence from randomized controlled trials addressing the effect of PSA screening on prostate cancer and all-cause mortality would likely shed some light on this debate. Two such studies are currently underway (the prostate, lung, colorectal, and ovarian cancer screening trial[19] and the European screening study for prostate cancer[20]), but their results will not be available until 2006. Without this information, physicians need to address the concerns of their male patients, and help them to make informed decisions about the role of PSA screening in their health care practices. This case also points to the importance of the other characteristics of a maneuver in setting recommendation levels. In this case, the lack of understanding about the natural history of the condition, the potential for unnecessary investigation, and the labeling effects of having a positive test play important roles in the final decision to exclude PSA screening from the Periodic Health Examination.

CASE # 5
COLONOSCOPY IN MEN AND WOMEN OVER AGE 40 WITHOUT A FAMILY HISTORY FOR COLORECTAL CANCER SCREENING

LEVEL OF EVIDENCE

The evidence for colon cancer screening by colonoscopy alone in asymptomatic individuals with no family history exists in the form of small case series.[21]

WHAT THE EVIDENCE SHOWS

Since these studies have no control groups or follow-up, there is no true direct evidence for or against the effectiveness of colonoscopic screening of asymptomatic individuals.[21]

TASK FORCE RECOMMENDATION: **C**

Since there is no concrete evidence (level III evidence in the form of case series) for or against the use of colonoscopy alone as a screening tool for colorectal cancer, the Task Force cannot make a recommendation to include or exclude this maneuver in the Periodic Health Examination.

KEY POINTS

This case is an example of a maneuver for which there is no true recommendation. Unfortunately, there are many maneuvers with *C* recommendations, which speaks to the lack of evidence that exists for many of the maneuvers that are commonly included in the Periodic Health Examination. In general, when faced with a *C* recommendation, there are some helpful tips that can guide decision making.[2] These include:

1. increasing patient involvement in decision-making
2. minimizing harm
3. advocating major change only on strong proof of need
4. avoiding unnecessary labeling
5. avoiding expensive maneuvers of unclear benefit
6. focusing on conditions with a high burden of illness
7. being attentive to special needs of high risk groups

Conclusion

The Canadian Task Force Periodic Health Examination plays an important role in both primary and secondary prevention practices in Canada. A clear understanding of the recommendation guidelines and their derivation is essential for the proper implementation of preventive maneuvers in every day practice. Although recommendations supported by good evidence should almost always be followed, the guidelines with fair or no evidence require careful consideration in the greater context of the patient and their unique presentation.

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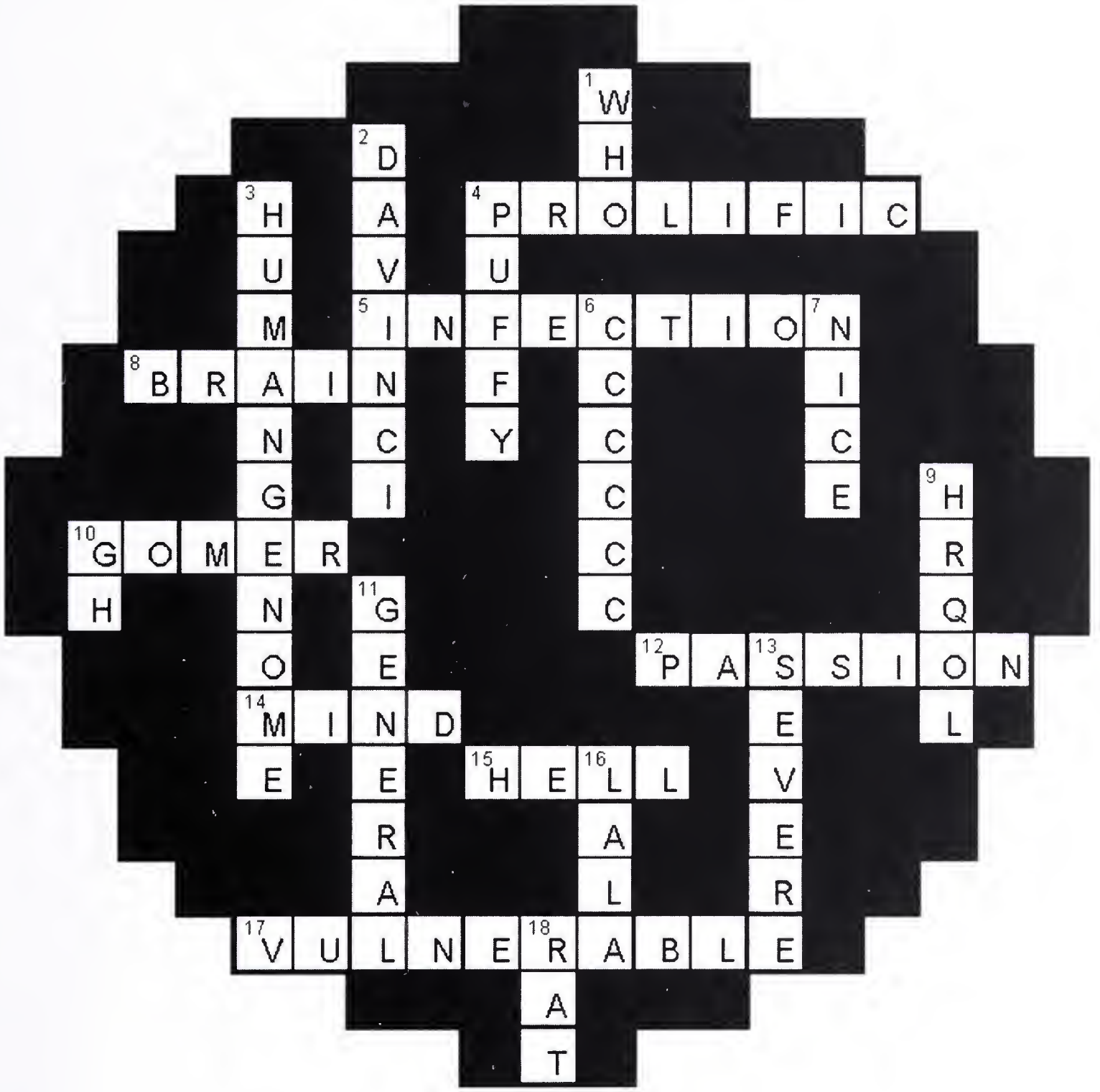
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Back to Basics VI

An Approach to the Patient with a Life-Threatening Acid-Base Disturbance: the Alkalemias and Mixed Disturbances

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This article is the second installment of a two-part series that addresses acid-base disturbances. Whereas the first discussed acidemias, this article will describe alkalemias and mixed acid-base disturbances.

As with the first installment in this series, the focus of this article is the identification of life-threatening acid-base disturbances. Despite the fact that disturbances of acid-base homeostasis are caused by a large number of medical conditions, very few pose an immediate danger to the patient's life. However, the identification of the life-threatening conditions is extremely important if they are to be managed quickly and appropriately, and thus, the emphasis of this article is on the identification of such situations.

As discussed in the first part of this series, disturbances of acid-base homeostasis can potentially cause life-threatening changes in organ and tissue function. However, it is usually the underlying cause, and not the acid-base disturbance itself, that is life-threatening. In many cases, the acid-base changes simply serve as symptoms of the underlying condition. Thus, the goal of this article is to provide a systematic approach to acid-base disturbances, specifically the alkalemias and mixed disorders, such that the underlying cause can be appropriately identified.

Systematic Approach to the Identification of an Acid-base Disturbance

Identifying the type of acid-base disturbance present and determining the underlying cause of this disturbance requires a systematic approach to ensure that important aspects are not overlooked. The approach provided below is identical to that described in the first installment of this series. We have provided it again to remind the reader that this approach should be used for all acid-base disturbances (Table 1).

Table 1
Systematic approach to the identification of an acid-base disturbance

Step 1	Establish the clinical context
Step 2.	Examine the four major lab measurements – pH, $PaCO_2$, $[HCO_3^-]$, and Plasma Anion Gap
Step 3	Examine other lab measurements

Step 1 – Establish the Clinical Context

An assessment of the clinical situation will provide an indication of the urgency of the patient's condition. Additionally, a careful history and physical examination, along with examination of past medical records, is essential because the clinical information obtained is extremely valuable in determining the underlying cause of the disturbance. The extensiveness of this assessment must be appropriate for the urgency of the clinical situation.

Step 2 – Examine the four major lab measurements – pH, $PaCO_2$, $[HCO_3^-]$, and plasma anion gap

Examining these four parameters allows one to identify and characterize the primary acid-base disturbance and to identify the presence of concurrent secondary disturbances (mixed acid-base disorders).

Table 2
Normal laboratory values

	Normal Range	Units
Arterial blood gases (ABG)		
pH	7.38 – 7.42	
$PaCO_2$	37 – 43	mm Hg
PaO_2	90 – 100	mm Hg
SaO_2	95 – 98 %	
$[HCO_3^-]$	22 – 28	mmol/L
$[H^+]$	38 – 42	nmol/L
Serum electrolytes		
$[Na^+]$	135 – 145	mmol/L
$[K^+]$	3.5 – 5.1	mmol/L
$[Cl^-]$	98 – 106	mmol/L
Osmolality	280 – 300	mOsm/kg

(i) Identifying the primary disturbance

Begin by identifying the most abnormal value (normal values presented in Table 2), which will provide direction as to which disturbance is present. Changes in the pH clearly identify acidemias

versus alkalemias, and large changes in the [HCO_3^-] are suggestive of metabolic disorders. Examination of all values together will then allow confirmation of which disorder is present (Table 3).

Table 3
Characteristics of acid-base disturbances

Disturbance	Identifying Characteristics
Metabolic Acidosis	Low pH
	Low [HCO_3^-]
Respiratory Acidosis	Low pH
	High $PaCO_2$
Metabolic Alkalosis	High pH
	High [HCO_3^-]
Respiratory Alkalosis	High pH
	Low $PaCO_2$

(ii) Using the plasma anion gap

An increased plasma anion gap (PAG) is usually a sign that there has been overproduction, addition, or retention of an acid in plasma. The "gap" increases because of the presence of the acid's unmeasured conjugate base (an anion) in plasma.

If the PAG is increased, it should be compared with the change in [HCO_3^-]. For every 1 mEq/L of conjugate base anion present in plasma, expect a 1 mEq/L increase in the PAG and a 1 mmol/L decrease in [HCO_3^-]. If the difference in magnitude of rise in PAG compared with the magnitude of the fall in [HCO_3^-] is greater than 5 mmol/L, a second disturbance may be present.

An increased PAG may be the only clue that there is an acid-base disturbance present (i.e., in a mixed acid-base disturbance with a normal pH). Additionally, in a patient with a primary acid-base disturbance other than metabolic acidosis, an increased PAG suggests the presence of a concurrent metabolic acidosis.

(iii) Examining the expected physiological response

A primary disturbance results in a physiological response by the body to return the [H^+] towards normal. Particular responses are expected and if the observed response is inadequate or inappropriate, this may indicate the presence of a secondary disturbance (Table 4).

Step 3 – Examine other lab measurements

Measurements such as the plasma osmolal gap, urine electrolytes, urine osmolal gap, urine net charge, and urine pH may be useful in determining the underlying cause of the acid-base disturbance. The uses of these measurements are outlined in Table 5 and are described in more detail in the appropriate sections of this article.

Metabolic Alkalosis

The most obvious features of metabolic alkalosis occur in the extracellular fluid — an increase in [HCO_3^-] and a decrease in [H^+]. However, to fully understand how the alkalemia developed and how to treat its underlying cause appropriately, the renal response to an increased [HCO_3^-] and events occurring in the intracellular fluid (ICF) must be examined. Accordingly, these aspects of metabolic alkalosis are discussed below.

The two most common causes of metabolic alkalosis are protracted vomiting (overt or surreptitious) and diuretic use in someone consuming a low salt diet. With both of these causes, life-threatening situations can result as a consequence of hypokalemia (e.g., ventricular arrhythmias, profound muscle weakness)[1] and possibly extracellular fluid (ECF) volume contraction. For these reasons, these situations require immediate recognition and treatment. As discussed below, the key to the identification of these causes of metabolic alkalosis is the examination of the urine [Cl^-].

Causes

Vomiting

When HCl is lost through vomiting, Cl^- is lost from the ECF, creating a state of Cl^- depletion. To maintain electroneutrality, HCO_3^- is effectively added to the ECF in conjunction with the loss of H^+ in the stomach. With time, the mass balance changes — the deficit of HCl is converted to a deficit of KCl.[2] This K^+ loss is renal in origin and is due to the delivery of Na^+ to the cortical collecting duct (CCD) without Cl^-, together with an avidity to reabsorb Na^+. In this state of Cl^- depletion, the majority of Cl^- is reabsorbed proximally so Na^+ is delivered distally with other anions such as HPO_4^- and SO_4^{2-}. While Na^+ is reabsorbed distally, anions other than Cl^- and HCO_3^- are not, creating a negative CCD lumen voltage.[3]

The anions remaining in the lumen require an accompanying cation to be excreted. The possible choices are NH_4^+ or K^+; however, NH_4^+ is not normally present in sufficient amount because

Table 4
Expected physiological responses to acid-base disturbances

Primary Disturbance	Expected Response	
	Mechanism	Magnitude
Metabolic Alkalosis	Hypoventilation	Drop the 7 and the decimal point from the pH to get the expected $PaCO_2$
Respiratory Alkalosis	*Acute*: shift in the BBS to consume more HCO_3^-	For each 10 mmHg fall in the $PaCO_2$, the [HCO_3^-] should fall by 2 mmol/L
	Chronic: decreased renal generation of HCO_3^-	For each 10 mmHg fall in the $PaCO_2$, the [HCO_3^-] should fall by 5 mmol/L
Metabolic Acidosis	Hyperventilation	For each 1 mmol/L decrease in [HCO_3^-], the $PaCO_2$ should decrease by 1 mmHg.
Respiratory Acidosis	*Acute*: shift in the BBS to produce more HCO_3^-	For each 10 mmHg rise in the $PaCO_2$, the [HCO_3^-] should rise by 0.8 mmol/L
	Chronic: renal generation of HCO_3^-	For each 10 mmHg rise in the $PaCO_2$, the [HCO_3^-] should rise by 3 mmol/L

Table 5
Useful measurements for the analysis of acid-base disturbances

Measurement	Equation	Normal Value	Use
[illegible] Equation	$[H^+] = (24\ PaCO_2) / [HCO_3^-]$	—	Checking for lab errors Calculated and reported values should coincide
Plasma Anion Gap PAG	$[Na^+] - [Cl^-] - [HCO_3^-]$	12 ± 2 mEq/L	Detects the accumulation of acids in plasma (excluding HCl and H_2CO_3)
Plasma Osmolal Gap POG	Measured Osmolality – Calculated Osmolality Calculated Osmolality = $2[Na^+]$ + [Glucose] + [Urea]	< 10 mOsm/L	Detects the presence of alcohols in plasma
Urine Osmolal Gap (UOG)	Measured Osmolality – Calculated Osmolality Calculated Osmolality = $2([Na^+]+ [K^+])$ + [Glucose] + [Urea]	—	Yields an estimate of the $[NH_4^+]$ in urine
Urine pH	Measured value	—	Detects a deficit in renal NH_3 production and/or H^+ secretion

Table 6
Conditions causing metabolic alkalosis[3, 5]

Conditions associated with low urine $[Cl^-]$ (< 20 mmol/L)	Conditions associated with high urine $[Cl^-]$ (> 20 mmol/L)
• Loss of gastric contents (vomiting, nasogastric suction)	• Recent diuretic use
• Remote diuretic use	• Conditions associated with diuretic-like activity: Bartter's syndrome, hypercalcemia, gentamycin use
• Non-reabsorbable anions when there is a Cl^- deficit	• Enhanced mineralocorticoid activity
• Post-hypercapnia with a Cl^- deficit	- Primary aldosteronism
• Gastrointestinal loss of NaCl (congenital chloridorrhea, some villous adenomas)	- Secondary hyperaldosteronism (e.g., renal artery stenosis)
• Cystic fibrosis (high sweat chloride)	- Endogenous or exogenous mineralocorticoids

NB metabolic alkalosis can be seen in patients with renal insufficiency (assuming that their diet contains sources of HCO_3^-). This has not been included in this table, however, because the diagnosis would be obvious from the clinical presentation and the plasma creatinine, and not via examination of the urine $[Cl^-]$.

of the alkalemia. Therefore, with the negative CCD lumen voltage, a gradient is created for increased secretion of K^+. The loss of K^+ occurs from the ICF, and when K^+ exit cells, a major ECF cation must enter in exchange to maintain electroneutrality. In the absence of significant ECF volume contraction, this cation is H^+, which creates an intracellular acidosis in addition to a decreased ICF $[K^+]$.[4] If an ECF volume contraction exists, some of the cations entering the ICF will be Na^+ in addition to H^+. Intracellular acidosis occurs in PCT cells and results in increased NH_4^+ and HCO_3^- production. Once NH_4^+ production has risen, K^+ is longer secreted in excessive amounts. This is reflected by the fact that with recent vomiting, the urine $[K^+]$ is quite high, while with remote vomiting the urine $[K^+]$ is not elevated.[3]

Diuretics

Metabolic alkalosis can result from diuretics such as thiazides and loop diuretics (those that do not cause bicarbonaturia).[5] The excess HCO_3^- in the ECF are generated via an increase in renal NH_4^+ production and excretion, which is the result of diuretic induced hypokalemia. Diuretics cause excretion of Na^+ and Cl^-, resulting in a Cl^- depletion and a decrease in the ECF volume that results in activation of the renin-angiotensin-aldosterone system. The increased flow in the CCD and the action of aldosterone increase the excretion of K^+. In this setting of KCl depletion and hypokalemia, K^+ exits the ICF in exchange for H^+ (to maintain electroneutrality), resulting in intracellular acidosis and worsening of the alkalemia. Intracellular acidosis of proximal convoluted tubule (PCT) cells causes the increased NH_4^+ and HCO_3^- production. As in the case of vomiting, electroneutrality in the ECF is maintained via the loss of Cl^- and addition of HCO_3^-.

Renal mechanisms contribute to the increased $[HCO_3^-]$ in the ECF. PCT intracellular acidosis, along with the activity of angiotensin-II, increases HCO_3^- reabsorption.[3] The ECF volume contraction results in a reduced glomerular filtration rate (GFR), which lowers the filtered load of HCO_3^-, further contributing to the maintenance of the increased plasma $[HCO_3^-]$.[3]

The events occurring in the ICF cannot be forgotten in this explanation. The loss of K^+ from the ICF is the cause of the increased NH_4^+ and HCO_3^- production in the PCT and the increased HCO_3^- reabsorption. Correcting this deficit is an important aspect of treatment.

Identification

The history and physical examination yield important information and are described below. However, the key to the identification of the underlying cause is examination of the urine $[Cl^-]$. With the causes discussed above, the patients will be Cl^- depleted. Thus, one should observe Cl^--free urine, as most of the filtered Cl^- will have been reabsorbed by the kidney. Examination of the urine $[Cl^-]$ is extremely useful in making the diagnosis because many

patients will not admit to diuretic abuse or self-induced vomiting. The diagnosis can and must often be made by examination of the urine [Cl^-] from a single or several random urine samples.[3]

In the setting of vomiting (recent or remote) or remote diuretic use, one expects to observe a low urine [Cl^-] (<20 mmol/L). If the [Cl^-] is high in the setting of metabolic alkalosis, there are three possible explanations:

- Recent diuretic use — the urine [Na^+] and [Cl^-] are high due to the diuretic;
- Conditions associated with diuretic-like activity (e.g., Bartter's syndrome, hypercalcemia, gentamycin use);
- Conditions associated with enhanced mineralocorticoid activity (Table 6).

A careful history should be taken, with inquiry into a patient's use or abuse of diuretics and history of vomiting (medically related or self-induced). Many patients will not directly admit to the abuse of diuretics or self-induced vomiting; nonetheless, inquiry into the patient's eating habits, body image, and psychosocial issues may yield important information.

On examination, signs of surreptitious vomiting, such as blackened tooth enamel and scarred knuckles, should be looked for.[5] In addition, one should look closely for signs of significant ECF volume contraction (decreased jugular venous pressure, orthostatic hypotension, and tachycardia). Patients who have abused diuretics will almost always have a contracted ECF volume while those who have vomited may or may not. However, even if ECF volume contraction is present in either scenario, it may only be subtle and may defy clinical detection.

Management

The management of the patient with metabolic alkalosis due to vomiting or diuretic use will depend on the urgency of the clinical presentation. The life-threatening complications of hypokalemia, such as cardiac arrhythmias, or the complications of ECF volume contraction will require immediate attention if present. If such conditions are not present, the patient must be treated to prevent these complications from occurring.

The basis of treatment involves treating the underlying cause, not the alkalemia itself. Patients with metabolic alkalosis due to vomiting or diuretic use are K^+ and Cl^- depleted (almost all patients will be hypokalemic). Thus, treatment involves correction of these deficits. The K^+ deficit is most often corrected by administration of KCl, which simultaneously corrects the Cl^- deficit. NaCl administration is required in addition to KCl only if the patient's ECF volume is contracted.

Correction of the underlying cause of the electrolyte disturbance that led to the alkalosis is essential for preventing the situation from occurring again. Alteration of diuretic therapy may be required and medically related vomiting must be stopped. If either diuretic abuse or induced vomiting is the cause, psychotherapy may be required.

For those conditions that involve high urine [Cl^-], the acute complications of hypokalemia must also be dealt with first. Treating the underlying cause involves replacement of the Cl^- deficit (these patients excrete excess Cl^-) and whichever cation deficit is present. Because these conditions are not very common, they are not discussed here.

Respiratory Alkalosis

Respiratory alkalosis is characterized by a high pH and lower than expected $PaCO_2$. In evaluating $PaCO_2$ levels, consider the appropriate physiological response if another acid-base disturbance is present.

In respiratory alkalosis, the low $PaCO_2$ causes the BBS equilibrium to shift to the right, away from H^+ and HCO_3^-.

$$H^+ + HCO_3^- \rightleftharpoons CO_2 + H_2O$$

A more significant decline is seen in [H^+] than [HCO_3^-] because of the million-fold difference in their relative plasma concentrations. This explains the significant rise in pH and small drop in HCO_3^- associated with acute respiratory alkalosis. If the respiratory alkalosis persists, the kidney responds to the alkalemia by reducing HCO_3^- production, which shifts the BBS equilibrium leftward; this raises the [H^+] toward its normal value.[3] The expected HCO_3^- and $PaCO_2$ values of acute and chronic respiratory alkalosis are outlined in Table 4.

Table 7
Conditions causing respiratory alkalosis [3]

Hypoxia	Pulmonary receptor stimulation	CNS disorders	Drugs	Other
• High altitude	• Asthma	• Subarachnoid hemorrhage	• Salicylates (most common)	• Anxiety-induced hyperventilation
• Pulmonary disease	• Pulmonary embolism	• Cheyne-Stokes respiration	• Catecholamines	• Cirrhosis
• Congestive heart failure	• Pulmonary fibrosis	• Primary hyperventilation syndrome	• Theophylline	• Fever
	• Pneumonia		• Progesterone	• Gram-negative sepsis
	• Pulmonary edema		• Nikethamide	• Pregnancy

Table 8
Identification of mixed disorders (if the pH is normal)

If the pH is normal, any of the following suggest the presence of a mixed disorder

1. The $PaCO_2$ and the [HCO_3^-] are both low (respiratory alkalosis and metabolic acidosis).
2. The $PaCO_2$ and the [HCO_3^-] are both high (respiratory acidosis metabolic alkalosis).
3. The PAG is increased by more than 5 mmol/L (metabolic acidosis plus an alkalemia).

Table 9
Identification of mixed disorders (if the primary disturbance is metabolic)

To detect coexistent respiratory disorder	To detect coexistent metabolic disorder
1 Examine the $PaCO_2$ 2 If it is much higher than expected, there is a coexistent respiratory acidosis 3 If it is much lower than expected, there is a coexistent respiratory alkalosis	1 If the PAG is increased, the patient likely has a metabolic acidosis 2 If the rise in the PAG is much greater than the fall in the $[HCO_3^-]$, this indicates a source of $[HCO_3^-]$—that is, a coexistent metabolic alkalosis 3 If the rise in the PAG is less than the fall in the $[HCO_3^-]$, this indicates loss of $[HCO_3^-]$—that is, a coexistent metabolic acidosis caused by loss of $NaHCO_3$ or renal tubular acidosis

Table 10
Identification of mixed disorders (if the primary disturbance is respiratory)

To detect a coexistent metabolic disorder
1. Examine the $[HCO_3^-]$ and determine if the respiratory condition is acute or chronic. 2. If it is much higher than expected, there is a coexistent metabolic alkalosis. 3. If it is much lower than expected, there is a coexistent metabolic acidosis.

Table 11
Identification of a mixed acid-base disorder—an example

Time		t_1	t_2	t_3
Condition Added	Normal	DKA	Vomiting	Aspiration
Category		Metabolic Acidosis	Metabolic Alkalosis	Respiratory Acidosis
pH	7.40	7.25	7.40	~7.27
$[HCO_3^-]$	25	**10**	**25**	~26
PCO_2	40	25	40	**60**
PAG	12	**27**	27	27

Causes

Respiratory alkalosis is defined as excessive ventilation. Carbon dioxide is a major respiratory stimulant that acts directly on central chemoreceptors.[6] Other ventilatory triggers that can induce hyperventilation include hypoxia, increased afferent activity, anxiety, and various drugs such as theophylline, methylxanthine, and aminophylline.[7]

There are many possible underlying causes of respiratory alkalosis. Some are serious such as asthma, lung disease, and liver failure. Commonly, however, the cause is psychogenic. Although not an medical urgency, anxiety-induced chronic hyperventilation can be quite debilitating and disruptive for individuals with anxiety disorders. Table 7 provides a list of conditions that can cause respiratory alkalosis.

In emergency situations, however, the most important cause of acute respiratory alkalosis is aspirin overdose. Given the purpose of this article, our focus will be on severe salicylate intoxication.

Salicylates

Many common, over-the-counter therapeutic products contain salicylates including acetylsalicylic acid (ASA or aspirin), Pepto Bismol and some topical ointments. These drugs are taken to treat headaches, inflammation, fever, and joint pain.[8]

Acetylsalicylic acid (ASA) contains an acetyl group linked to salicylic acid. The acetyl group is responsible for many of aspirin's therapeutic benefits, including anti-coagulation.[6] Salicylate has a pKa of 3.0 and almost completely dissociates into salicylate anion and H^+ within the body.[7] The ingestion of salicylic acid produces an alkaline pH despite this H^+ load because of salicylate's effect on the CNS, stimulating ventilation and thus lowering the $PaCO_2$. For this reason, the major acid-base disturbance with salicylate toxicity is respiratory alkalosis.

The respiratory alkalosis itself is not the life-threatening factor. Salicylates, when taken in excess, exhibit toxic effects: they may uncouple normal oxidative phosphorylation. As a result, the rate of production of adenosine triphosphate (ATP) falls and vital cell functions can become compromised. This raises metabolic rate and oxygen consumption. Salicylates also increase ketone pro-

duction and induce a degree of *L*-lactic acidosis, especially in children.[7]

Identification

Salicylate intoxication occurs because of accidental or intentional over-medication. Principally, those at risk for salicylism fall into three groups: the depressed and/or suicidal, young children, and the elderly.

In some instances, patients will report salicylate intoxication. Appropriate lab tests can confirm the diagnosis. However, when the diagnosis is not immediately apparent, patients may present with hyperpnea, delirium, agitation, tachycardia, tinnitus, and usually in children, an elevated anion gap metabolic acidosis.[7] A venous blood gas indicative of respiratory alkalosis, or a combination of respiratory alkalosis with mild metabolic acidosis should lead to the suspicion of ASA intoxication. An arterial blood gas is unnecessary, unless there is a special indication such as hypoxia.

A toxicology screen measuring toxic levels of salicylates is a definitive diagnosis. In severe salicylism, with serum salicylate levels of 70 mg/dl or higher, arrangements to start hemodialysis should be made immediately.[6]

Management

In all cases of salicylism, ASA input should be ceased. If aspirin ingestion has occurred within several hours, gastric lavage and the use of an adsorbent material may be applied to prevent further salicylate absorption.

If serum salicylate levels are below toxic levels, an alkaline diuresis may be employed to enhance salicylate elimination by renal excretion. Alkaline diuresis involves ECF volume expansion and in some cases, sodium bicarbonate infusion.[6] The rationale for expanding ECF volume is to decrease the production of angiotensin-II, which then directly decreases the reabsorption of bicarbonate at the kidney's proximal convoluted tubule. This helps augment salicylate elimination since bicarbonate competes with salicylate for renal excretion. An infusion of sodium bicarbonate should also enhance renal excretion of salicylate. However, there is a danger that the infused bicarbonate will worsen the alkalemia.[3] Thus, a physician should weigh the benefits and dangers carefully when deciding on this treatment.

With more severe toxicity, acetazolamide may be administered in very small doses to increase salicylate excretion.[3] However, in binding to albumin, acetazolamide may worsen the salicylate intoxication by increasing the amount of unbound salicylate in the serum. Thus, this treatment should not be aggressive and must be prescribed with extreme caution. In severe salicylate intoxication, hemodialysis is needed to remove salicylates from the body.

Mixed Acid-Base Disorders

When two or more acid-base disorders occur concurrently, a mixed disorder is said to be present. These disorders add another layer of complexity to acid-base disorders, but by following the systematic approach outlined above, one can confidently arrive at the correct diagnosis. Tables 8, 9, and 10 outline strategies to identify mixed disorders.

Realization that a mixed disorder exists often occurs during step 2 of the systematic approach, when the four major lab values are evaluated. Based on the numbers, something just doesn't "make sense". It may be difficult to identify the primary disturbance (Table 3), there may be an unexpected elevation in the PAG, or the expected physiological response (Table 4) may not be observed. In such a situation it is important to rule out a lab error. This can be done by using the Henderson equation; if the $[HCO_3^-]$ from the Henderson calculation differs from the reported $[HCO_3^-]$ by greater than 10%, an error has been made and the lab tests must be redone.

An example of a mixed disorder is presented in Table 11. The table presents lab values for a patient at three times in her clinical course. At time t_1 the disorder is purely a metabolic acidosis as indicated by the low concentration of bicarbonate and the correspondingly low pH. Also notice the expected physiologic response in $PaCO_2$ and elevated PAG that corresponds in magnitude to the decrease in $[HCO_3^-]$.

At time t_2 the DKA patient begins to vomit, which superimposes a metabolic alkalosis upon the original metabolic acidosis. In this example the magnitude of the metabolic alkalosis equals that of the original metabolic acidosis and re-establishes the $[HCO_3^-]$ at 25 mmol/L. As a result, the physiological response returns the $PaCO_2$ to its original value of 40 mmHg. Other than the PAG which remains elevated, no indication of an acid-base disorder remains. This highlights the importance of always calculating the PAG as part of the systematic approach.

Later, at time t_3, the patient has aspirated her vomitus, which then obstructs her airway and introduces a respiratory acidosis. The $PaCO_2$ rises sharply, resulting in the reduced pH. In addition, the expected physiologic response will increase the $[HCO_3^-]$ slightly in the acute setting.

Conclusions

Metabolic or respiratory alkalosis can be a sign of a medical emergency requiring immediate attention. The alkalosis itself is rarely life threatening, but by following the systematic approach outlined above, the characteristics of the acid-base disturbance can be exploited to guide the clinician to the correct diagnosis. Once the diagnosis is made, treating the underlying condition responsible for the production of the alkalosis is the key management strategy.

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Back to Basics VII

Minor Burns Injuries

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Abstract

Most burn injuries sustained by Canadians are minor and can be effectively treated in a primary care setting. A critical part of burn management is evaluating the depth and extent of injury. The American Burn Association has developed criteria for determining which patients can be managed on an outpatient basis. The approach to primary burn care can be conceptualized using the six "C's": clothing, cooling, cleaning, chemoprophylaxis, covering and comforting (i.e., analgesia). Follow-up care and patient education are critical for preventing infection and complications such as scar formation and contractures.

Introduction

Burn injuries can be devastating, resulting in lifelong disfigurement, dysfunction, psychological morbidity or even death. Each year, approximately 200,000 Canadians seek medical care for burns. The majority of burns occur at home, are minor, and can be effectively managed in a primary care setting.[1] For this reason, an approach to minor burn care is an essential clinical skill for a number of health care providers, including emergency physicians, general practitioners and nurses.

Ambulatory management involves accurate assessment of the severity of the burn, pain control, debridement and infection prophylaxis. In some instances, surgical referral is required. In all cases, the aim of treatment is to restore function and maximize cosmetic results.

Definition

As defined by the American Burn Association, a minor burn involves 5 to 10 percent of total body surface area and does not affect critical anatomical areas such as the hands, face, ears and perineum (Table 1).[2] Such injuries have negligible systemic effects and are unlikely to require surgical intervention. Patients who sustain a minor burn do not require admission to a burn centre and can be adequately managed in a primary care setting.

Pathophysiology

According to Jackson,[3] burn injuries may be conceptualized in concentric zones of cellular damage (Figure 1). The outermost area of injury, known as the zone of hyperemia, is analogous to a superficial burn. The adjacent inner area, known as the zone of stasis, represents poorly perfused tissue. This area of marginal injury has the potential for repair and normal function if perfusion is maintained and no further injury occurs; however, if the wound becomes very swollen or infected, this marginal zone can fail to repair itself, and result in a deeper wound.

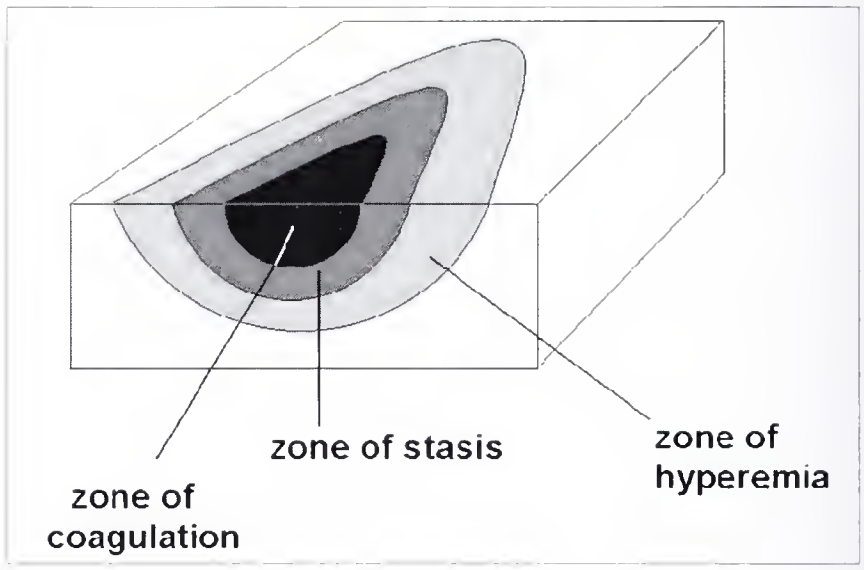

Figure 1. Jackson's zones of cellular damage following burn injury.

Finally, the innermost area of burn injury, known as the zone of coagulation, represents the area of cellular death. This pathologic description is significant because if the zone of coagulation is above the level of the dermal appendages (hair follicles, sebaceous and sweat glands), spontaneous healing can be expected. Conversely, if the zone extends below this level, the wound requires grafting for optimal results. Recognition of these zones is of great clinical significance. Following the initial injury, wounds may either heal spontaneously or show signs of increased depth and fail to heal on their own. For this reason, burn wounds must be reexamined approximately 24 hours after initial presentation.

Regardless of the mechanism of burn injury, once the integument is injured, the patient immediately begins to lose fluid via evaporation. A physiologic response of repair and restoration follows. Within minutes, microvascular and inflammatory

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responses are mounted and continue for up to several days after cellular damage occurs. Arachidonic acid metabolites, oxidants, histamine, serotonin, kinins and other vasoactive amines are released from damaged and ischemic cells. These inflammatory mediators cause leakage and sequestration of extracellular fluid in and around the burn site.[4] In partial-thickness burns, a serous exudate composed of plasma, leukocytes and fibrin often forms blisters or yellow sticky eschar (dead, coagulated skin). Approximately 48 hours following a partial-thickness burn, blood vessels begin to proliferate at the burn site, producing a new vascular network. The burn site is an ideal environment for the growth of microorganisms. Initially, the flora reflects that of normal skin and is composed of Gram-positive microorganisms; however, by the fifth day post-injury Gram-negative organisms predominate. Tissue destruction related to bacterial infection may cause less severe burns to evolve into deeper burns.

Evaluation of the Minor Burn Injury

Flame burns account for approximately 60% of adult minor burns and can occur at home (e.g., cooking, smoking, handling candles, house fires), or at the workplace (e.g., ignition of flammable gases or liquids, explosions, welding).[5]

Scald burns are the most common cause of minor burn injury in children, and are the second leading etiology in adults. Like flame injuries, scald burns may be sustained during a home activity (e.g., cooking, bathing, spilling hot liquids) or at work (e.g., handling hot liquids, or working with steam boilers).[5]

The pattern of injury observed on physical examination should corroborate the mechanism of injury elicited on history. If the pattern of injury fails to match the history, one must consider the possibility of abuse, neglect or arson. In such cases, the health care provider should note any discrepancies and suspicious features and, when appropriate, proceed with further questioning.

It is estimated that 9 to 11 percent of burns in children are the result of abuse.[6] Clues to intentional injury include immersion scalds ("stocking-glove" distribution), the presence of multiple, well-demarcated burn sites, and burns in varying stages of healing. If abuse is suspected, the proper authorities should be informed and hospital admission is warranted. In the case of self-inflicted burn injuries, psychiatric evaluation of the patient is necessary.

Patient's age

The skin of children younger than five years of age and adults older than fifty-five years of age is relatively thin and sustains deeper burn injuries than may be evident on initial examination.[7] For this reason, all burns in these age groups require closer observation. The social supports of the patient must also be assessed because they play an important role in determining his or her self-care abilities (e.g., dressing changes) and outcome.

Depth

Temperature and duration of exposure determine burn depth. Tissue destruction ensues above 40°C and increases exponentially with increasing temperature (Figure 2).[8]

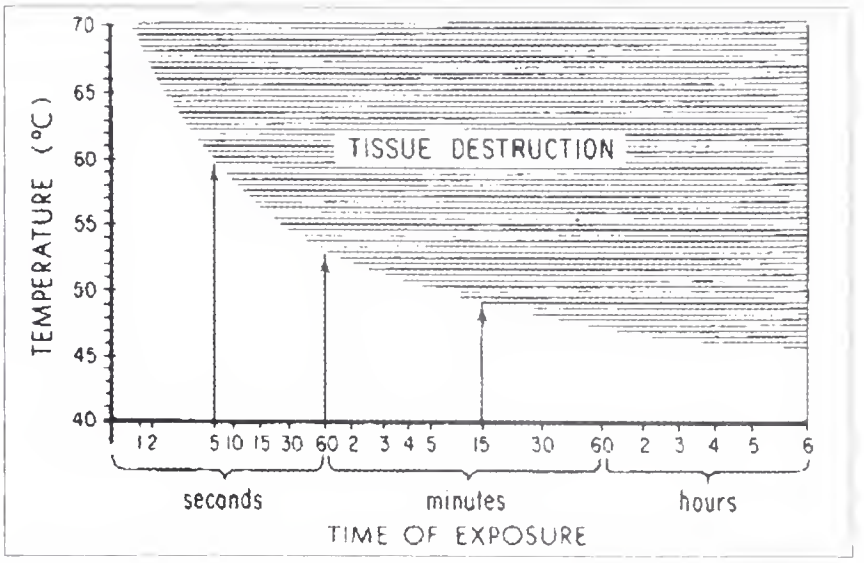

Figure 2. Relationship of exposure temperature and duration, and degree of tissue damage.

Table 1
American Burn Association Criteria for Minor Burns[2]

<10 percent TBSA burn in adult.
<5 percent TBSA in <10 years of age or >50 years of age
<2 percent full-thickness burn
TBSA = total percentage of body surface area affected by the injury

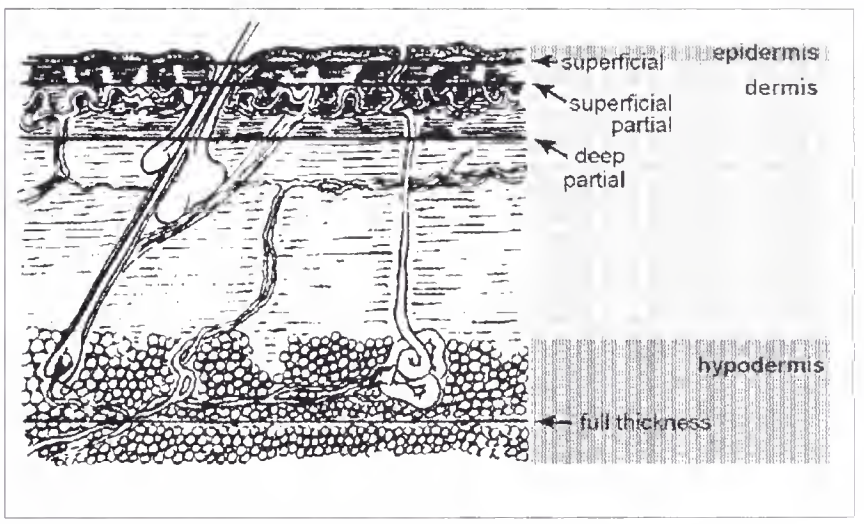

Figure 3. Burn depth and integumental layers.

Accurate determination of burn depth requires clinical experience. Within the first 24 hours following a burn injury, clinical assessments of burn depth by experienced burn care providers are accurate only 75% of the time.[10] The information provided in Table 2 is intended to act as a guide to the clinical features that distinguish burn depths. Often it takes 2–4 days until the burn depth becomes established. The wound appearance may change markedly during this time and is sometimes a surprise to both the patient and the clinician. The dynamic nature of these wounds is often not appreciated by primary care providers and sometimes leads to erroneous diagnoses. The opinion of the senior author is that the primary care physician should make an initial estimation of burn depth and inform the patient that the diagnosis may change over the next 2–4 days, thus avoiding the need to explain why the burn appears either better or worse than predicted from the initial examination.

Table 2
Burn Depth and Appearance[9]

Burn Depth	Morphology	Appearance	Sensation	Scarring
Superficial	Superficial epidermal layers only; congestion and dilatation of intradermal vessels	Red; blanches with pressure	Present	No
Superficial partial-thickness (SPTB)	Varying depth of destruction, sparing dermal appendages (hair follicles, sweat and sebaceous glands	Blisters; red, weeping and painful; blanches with pressure; superficial skin can be wiped away	Present, very sensitive in open air	Unusual, heals in less than three weeks
Deep partial-thickness (DPTB)		Colour variable; white with red elements (dermal vessels); wet or waxy dry; less painful than SPTB, does not blanch; can be difficult to distinguish from full-thickness burn	Deep pressure	Usually present
Full-thickness	Loss of all skin elements; thrombosis and coagulation of vessels	White or charred (sometimes red due to fixed hemoglobin); dry and inelastic; visible thrombosed vessels; no blanching with pressure	Deep pressure only	Present; risk of contracture

Figure 4a. Superficial burn to volar forearm.

Figure 4b. Superficial partial thickness burn to forearm. Note the presence of unroofed blisters.

Figure 4c. Deep partial thickness burn to palm. The wound has a wet, variable [illegible] with both pale and red areas.

Figure 4d. Full thickness burn to dorsum of hand. Thrombosed vessels and underlying adipose tissue are clearly visible.

Extent
The extent of burn injury is expressed as the pereentage of the total body surface area (TBSA) burned. Superfieial burns are not ineluded when ealeulating the proportion of TBSA affeeted. An estimate of the TBSA involved can be made for patients above the age of 10 years using the "rule of nines" (Figure 5). For patchy burns, it is also helpful to remember that the patient's palm represents approximatcly 1% of the TBSA.[11] In children below the age of 10 years, a Lund-Browder ehart should be used to determine TBSA affeeted.[12] Thesc charts are readily available in most emergency rooms.

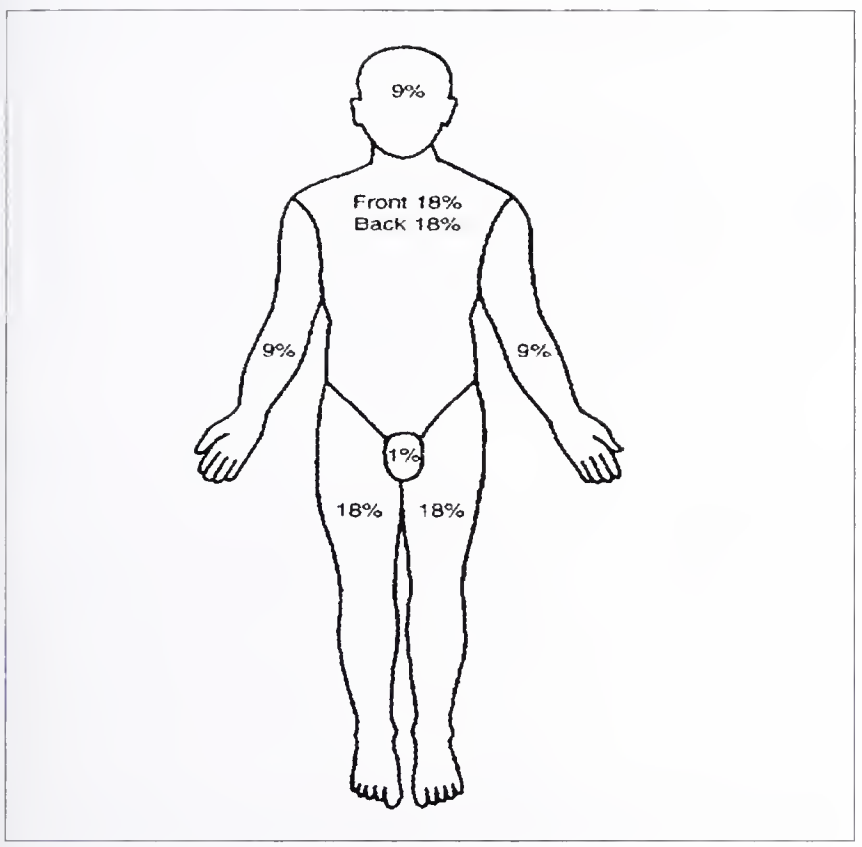

Figure 5. The "rule of nines" allows for rapid estimation of total body surface area involved in a burn injury.

Investigations
Unlike severe burn injuries, or those eomplicated by related injuries, minor burns require no investigations.

Management of the Minor Burn Injury
Aceording to Peate,[13] subsequent managcment of minor burn injuries may be thought of in terms of six "C's": clothing, eooling, eleaning, ehemopropylaxis, eovering and comforting (i.e., analgesia).

Clothing
Any burned or hot clothing should be removed immediately. Any items exposed to ehemicals should be removed to eliminate further contaet with the offending substanee. Non-adherent elothing should be cut away; adherent items should be removed by irrigation.

Cooling
Burns should be eooled as soon as possible following the initial insult. In most cases, the patient with burns is seen by the primary care physician well after the injury has cooled. Nevertheless, further eooling should be administered as it has been shown to decrease burn pain within the first several hours.[14] Patients will generally stop immersing the injured area once the pain is treated with analgesia. Some groups have suggested the use of sterile saline-soaked gauze at a temperature of about 12°C for cooling.[15] The senior author suggests that, in praetiee, eool water, whether 12°C or not, is effective in minimizing pain and comforts most patients. Sterile solutions are not necessary. Iee should never be used beeause it produees vasoconstrietion whieh reduees the vascular flow and may increase tissue damage. There are many home remedies for burns that range from toothpaste to "magic ereams," but the effeetiveness of such agents is unproven. The simple approach is to wash thc area with tepid water to ease the swelling and pain, and stop the burning proeess.

Cleaning
Cleaning a wound to remove dead tissue, such as blisters, and offending agents, sueh as tar or asphalt, is critical. Although a number of different eleansing agents continue to be used, growing evidcnce supports the use of mild soap and tap watcr alone for washing burns.[7,9,16,17] Disinfeetants such as ehlorhexidine glueonate solution (Hibiclens™) and povidone-iodine solution (Betadine™) are not recommended because they inhibit healing.[7] Cleaning is neeessary but may result in tremendous pain, particularly in superficial wounds. Use of oral nareoties (morphine or codeine) is usually suffieient to allow wound eare. If analgesia is administered in advance and given suffieient time to act, debridement of the wound will be less painful for the patient.

Mineral oil mixed with cool water may be used to remove substanees sueh as tar and asphalt. Residual tar may be emulsified and removed by repeated applieation of polymyxin B-baeitracin zinc ointment (Polysporin™). Polysporin™ should be applied for 2–3 hours, then wiped off and reapplied.

Necrotic tissue from partial- and full-thickness burns should be removed manually. Ruptured blisters should be debrided. Unroofing of intact blisters is reeommended if the blisters are infected, haemorrhagic or restrict range-of-motion.[18] It is all-too-eommon to eneounter patients with limited joint mobility owing to largc blisters that have been left intact. Blisters persisting for several weeks without resorption may indicate underlying partial- or full-thiekness burns or the presence of a comorbid eondition sueh as diabetes.[14]

Chemoprophylaxis
Tetanus immunization should be administered to all patients sustaining burns deeper than superficial partial-thickness.

Differentiating between the inflammatory response that follows a burn and an infectious proeess can be extremely difficult. Infection is often overdiagnosed and treated with parenteral antibiotics. It is important to remember that erythema extending beyond the wound margin represents a normal inflammatory response to the burn injury, not an infection. Infeetion should be suspected in cases where lymphangitis, fever, malaise and anorexia occur in eonjunetion with the erythema, edema and pain not in keeping with that level of burn injury, or in eases where these latter signs inerease steadily over a baseline level.[14]

Infection ean produee additional tissue damage, converting a

Table 3
Comparison of Commonly Used Topical Antimicrobial Agents[19]

	Polysporin™ (polymyxin B- bacitracin)	Flamazine™ (silver sulfadiazine)
Mechanism of action	Interrupts cell wall synthesis and cell membrane permeability	Interrupts intermediary metabolism
Advantages	Readily available over the counter Relatively inexpensive Clear, allowing for visualization of wound Easily applied	Broad spectrum antimicrobial activity (bactericidal effects on Gram-positive and Gram-negative bacteria and yeast) Soothing Non-toxic Easily applied
Disadvantages	Folliculitis Hypersensitivity reaction Narrow spectrum antimicrobial activity Prolonged use may result in overgrowth of non-susceptible organisms Potentially nephrotoxic, ototoxic if used in large amounts over large areas	Not widely available Relatively expensive Poor penetration of eschar may lead to proliferation of resistant bacteria Leaves a thick white-yellow exudate on wounds which may appear purulent May cause breakdown of intact skin May cause transient leukopenia

superficial partial-thickness burn into a deep partial-thickness burn. Furthermore, a burn wound can become a nidus of infection, in severe cases leading to sepsis. In such instances, hospital admission and parenteral antibiotic therapy are indicated.[16] This can be avoided with most minor burn injuries.

Such severe complications can be avoided with most minor burn injuries, through the administration of topical prophylaxis. All burn injuries except superficial burns require topical prophylaxis. The agent of choice depends on the wound depth and clinical ease of application. The two most commonly used agents are polymyxin B-bacitracin (Polysporin™) and silver sulfadiazine (Flamazine™) (Table 3).[19] To date, no formal studies have been conducted comparing the effectiveness of polymyxin B-bacitracin over silver sulfadiazine.[13]

Covering

No definitive recommendations exist with regard to covering minor burns.[14] Ideally, a covering should offer anaesthetic relief by reducing pressure on the wound, provide a barrier to infection and keep the wound dry by absorbing drainage. Superficial burns require no dressing and should be treated with a simple lubricant such as aloe vera. Partial- and full-thickness burns should be covered with a nonadherent dressing (eg.,Telfa™) applied over a thin layer of topical antibiotic cream. The nonadherent dressing should be held in place with tubular net bandage or lightly applied gauze wrap. Although recommendations for the frequency of dressing changes vary from twice daily to once a week, dressings should always be changed when they become soaked with exudate.[14] Topical antibiotic should be removed and reapplied with every dressing change. Patients should be encouraged to wash the wound regularly with soap and water and not to avoid showering or bathing.

Comforting

Even the most seemingly minor burns can produce an immense amount of pain. Control of baseline pain should be managed with acetaminophen (Tylenol™) in combination with a non-steroidal anti-inflammatory drug. Aspirin should be avoided due to its inhibition of platelet aggregation. Breakthrough pain during dressing changes or physical activity should be controlled with acetaminophen with codeine (Tylenol™ with Codeine) or morphine. Pain of greater than 5 (on a scale from 0 to 10) can interfere with daily dressing changes, activity, sleep and ultimately recovery.[20] Some injuries require large amounts of narcotic for short periods of time in order to allow wound healing to occur. As long as the patient can actively use the injured area and is not manifesting side effects of narcotic use, the use of narcotic analgesia should be encouraged. Underdosing is commonly seen because the degree of pain associated with even minor injury is often not fully appreciated.

Follow-up Care

Burn patients managed on an outpatient basis should be seen 24–48 hours following injury. At this visit, pain medication may be adjusted if necessary. The physician should also teach the patient and/or caregiver how to check the burn wound, how often to check it and how to avoid complications, such as impaired circulation due to overly tight elastic bandages. A primary care physician can perform subsequent follow-up on a weekly basis until wound epithelialization occurs. If pain is poorly controlled, or the patient's access to proper wound care is questionable, the patient should be seen on a daily basis until complete epithelialization takes place.[9,13] The patient should be referred to a burn surgeon if wound epithelialization fails to begin two weeks post-injury or if further visits reveal full-thickness burns of more than 2 cm in diameter.[9,14] Tiny opalescent islands of epithelium throughout the wound indicate epithelial-

ization, with complete wound healing occurring in the following one week to ten days.[14] All burns should be observed for at least six weeks for hypertrophic scars. These red, thick, raised, and often pruritic or painful scars are common in deep partial-thickness and full-thickness burns.

Primary care physicians should also be alert to the psychological sequelae of burn injury. Burn patients are at increased risk for depression, anxiety and posttraumatic stress disorder. Family members may feel a sense of guilt, while patients may develop dependency problems because of additional aid needed for activities of daily living. If a psychological problem is identified, treatment should be initiated after one month of persistent symptoms.[21]

Conclusion

The management of minor burns in a primary care setting presents a number of challenges. This article has aimed to provide a concise but comprehensive approach to the assessment and care of minor burns, in the hopes that it may prove useful to both students and established physicians.

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Furuncular Myiasis: A Case of an Unexpected Traveling Companion

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Case Presentation

A 34-year-old male presented to an outpatient walk-in clinic for assessment of a skin lesion on his right lower leg that began approximately 1 week prior as a painful, red bump. He was diagnosed as having a common bacterial boil, and treated with topical antibiotics and oral amoxicillin. Despite this intervention, the lesion persisted for another 3 weeks. In light of his unresponsiveness to antibiotic therapy and a recent history of travel to Belize, the patient was referred to the Centre for Travel & Tropical Medicine at the Toronto General Hospital for reassessment of his lesion. At the time of reassessment, the patient described in detail the evolution of his lesion over the previous 4 weeks. Over the course of his antibiotic treatment, the lesion progressed from a small, painful bump to a larger (1-cm diameter), raised, red lesion that periodically drained serosanguineous fluid (Figure 1). He complained of a sensation of movement within the lesion, and of stabbing pains that accompanied this sensation. In the 3 days prior to his reassessment, the lesion and the surrounding skin had become increasingly red and swollen, though the patient did not complain of fever, chills, sweats, or inguinal tenderness.

Past medical history, family and social history were non-contributory. Physical examination was unremarkable except for the presence of a fixed, indurated, erythematous, 1-cm diameter nodule on the patient's right lower leg. The nodule had a central punctum of approximately 2 mm in diameter through which serous fluid drained. Considerable surrounding cellulitis was present, as was edema up to the knee. The patient was afebrile with no evidence of inguinal lymphadenopathy. A swab of the lesion was taken for culture and sensitivity analysis, and the patient was placed on cloxacillin 500 mg q.i.d. An occlusive dressing was placed over the lesion, and the patient was discharged home with the understanding that he would return in 24 hours for re-evaluation and further treatment.

What is the differential diagnosis of a fixed, painful, erythematous nodule in a returning traveler?

Review of Skin Lesions in Returning Travelers

In evaluating skin diseases of the recently returned traveler, a lesion-oriented approach can be taken.[1] Skin lesions can be categorized into broad morphological patterns including papules, papulosquamous lesions, subcutaneous swellings and nodules, ulcers, linear and migratory lesions, and disorders of pigmentation.[1] Papules typically arise from the bite of arthropods such as mosquitoes, midges, fleas, and bedbugs.[1] They are often pruritic, and can be quite painful when the result of a black fly, scorpion, or spider bite.[1] Scabies, a disease caused by the ubiquitous mite *Sarcoptes scabiei* and characterized by papules that are distributed in the digit webs and genitalia, has a classic pattern of nocturnal pruritus, which may help distinguish it from other papular eruptions. Papulosquamous lesions are most often the result of aggravation of a condition with which the traveler left, such as eczema or psoriasis, but can also arise from superficial fungal infections (dermatophytosis).[1] A hallmark of dermatophyte infection (tinea corporis, cruris, or pedis) is scaling of the skin, and this can be accompanied by erythema, pruritus, and nail involvement.[1]

Subcutaneous swellings or nodules can be further categorized into lesions that are fixed and painful, fixed and painless, or migratory in nature. Fixed and painful nodules can occur in travelers because of persisting bacterial boils, or more interestingly, because of infestation of the skin by maggots or the adult female flea, *Tunga penetrans*.[1] Chagas disease, caused by *Trypanosoma cruzi*, can also have an initial dermatologic presentation in the form of a painful nodule or 'chagoma'. In the case of Chagas disease, the chagoma represents an acute stage of local multiplication of trypanosomes where they entered the body.[2] Although extremely rare in returning travelers, fixed, painless subcutaneous nodules can arise from infection with *Onchocerca volvulus* (the filarial nematode causing River Blindness in Africa and South America), or cysticerci (larval tapeworms that are found worldwide).[1,3,4] A considerable amount of space can be occupied by these worms, and thus, these fixed, painless nodules can be quite large. In the case of *O. volvulus*, nodules must be capacious enough to house a coiled adult worm of up to 50 cm in length.[3] Migratory subcutaneous swellings, also very rare in the returning traveler, are most often caused by another filarial worm, *Loa loa*. Endemic to West Africa, clinical signs of loiasis typically present several months after being bitten by an infectious deer fly.[1,3] Migration followed by stasis of the adult worm in the subcutis produces characteristic localized areas of angioedema referred to as 'Calabar swellings'. In addition to these classic nodules, the worm also makes its identity known by visibly migrating through the conjunctiva,[1,3] an occurrence that may engender a considerable amount of distress in the host.

Cutaneous ulcers are yet another type of skin lesion that can present in returning travelers. Ecthyma, a painful shallow ulcer that

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cellulitis from secondary bacterial infection of a traumatic skin wound (including insect bites), is the most frequently reported ulcer in travelers. Common etiologic agents are *Staphylococcus aureus* and group A *Streptococcus*. Pyodermas caused by β-hemolytic *Streptococcus* are also common. Unlike the painful bacterial ulcers, the ulcer caused by the more rare cutaneous leishmaniasis is often painless.[1]

Linear and migratory lesions often represent migration of parasitic worms through the skin and subcutaneous tissue.[1] Unlike loiasis, in which subcutaneous swellings indicate a temporary cessation of migration, erythematous serpentine tracks often follow the migratory route of geotropic larval nematodes that are in the wrong host. Cutaneous larval migrans, for example, is caused by animal hookworm larvae that penetrate the foot or buttocks of a human, and constitutes an intensely pruritic, red serpiginous lesion.[3] It is the most common of these lesions, accounting for one quarter of the reported dermatologic problems in returning travelers.[1] Although the list of pigmentation disorders is long, the most commonly reported in travelers to the tropics is pityriasis (tinea) versicolor.[1] This superficial fungal infection leads to the appearance of scaling, well defined, hyper- or hypopigmented lesions. The characteristic lesions are most often localized to the upper trunk and neck.[1]

Although the classification system described is independent of factors such as patient occupation, travel history, length of stay abroad, lesion location, progression of the lesion, and exposure history, these details should be elicited from the patient's history and are essential to narrowing the differential diagnosis. Occupational history is particularly relevant in diagnosing skin diseases, as the more exotic dermatoses are generally acquired by adventure-seekers who travel to rural areas, or by those whose employment necessitates work in the field.[1] Field workers such as veterinarians, health care providers, archeologists, and construction workers are far more likely to come in contact with vectors and agents of exotic diseases than are the average holiday or business travelers.[1]

Location of the lesion is another feature that is useful in constructing the differential diagnosis. Most arthropod vectors have a predilection for exposed skin (due to its convenience), and some have a further preference for the lower extremities, or parts of the body that come in contact with the ground (ticks and fleas, for instance). Conversely, certain aquatic skin disorders such as sea bather's eruption, are characterized by lesions that are distributed in areas covered by clothing.

While the geography of travel will give vital clues pertaining to the endemicity of etiologic agents and vectors, length of foreign travel is also an important determinant of risk for certain diseases. For example, diseases such as leprosy, filariasis, and yaws are most often seen in immigrant populations, and rarely in short term travelers.[1] Other historical details, such as incubation period or onset of symptoms, can be particularly helpful when the morphologic approach to diagnosing a lesion is insufficient. Like many other rashes, sea bather's eruption is intensely pruritic and papular, however, a distinguishing feature is that it occurs within minutes to hours of contact with salt water.[1]

In assembling a differential diagnosis of a skin disease in a returning traveler, it is therefore important to combine the morphological features of the lesion with historical details. Following a lesion-oriented approach with incorporation of data such as occupational history, location and duration of travel, exposure history, and progression of the lesion will ensure the generation of a focused yet comprehensive differential diagnosis.

Differential Diagnosis

Myiasis, Tungiasis, Furunculosis

In the case reported herein, the patient's lesion had evolved over a period of several weeks into a fixed, painful, subcutaneous nodule. To recap, the lesion was raised, red, elicited a sensation of movement, and had a punctum from which serosanguineous fluid drained (Figure 1). Thus, the most likely diagnoses were, in descending order, myiasis, tungiasis, and furunculosis (see Table 1 for comparison). A furuncle, or boil, is a deep inflammatory nodule, that usually develops secondary to inflammation of a hair follicle (folliculitis).[5] Furuncles occur in areas of the skin that have hair, and are exposed to both perspiration and frictional forces.[5] Such areas include the neck, face, axillae, and buttock. Furuncles begin as small, firm, tender, red nodules that over a few days, progress to hot, painful indurated lesions of 1 to 2 cm in diameter.[5] Upon rupture of the boil (either spontaneously or surgically induced), drainage of pus occurs. *Staphylococcus aureus* is a common isolate. After liberation of the purulent discharge, inflammation rapidly subsides and the lesion heals.[5] Treatment with cloxacillin will also lead to resolution of the boil. There were several characteristics of the lesion in question that made a diagnosis of furunculosis unlikely. First, the lesion was in an atypical location for a furuncle. Second, the lesion persisted for several weeks as opposed to days, and the drainage was serous not purulent. In addition, the patient's lesion had a central opening, which would have alleviated the pressure buildup that causes such intense pain with furuncles. Finally, the intermittent stabbing pain and sensation of movement reported by this patient are unlikely to be caused by a boil, which generally causes unrelenting pain until its rupture.

As previously mentioned, the sand flea *Tunga penetrans*, also known as the 'jigger', can cause fixed, painful nodules in those who become infested. Tungiasis has a widespread distribution with endemicity in South and Central America, Africa, and India. Tungiasis accounts for 6% of reported skin lesions in travelers.[1] The lesion itself is caused by invasion of the epidermis by the adult female, which generally penetrates the skin of the feet and around the toenails.[1,6] Thus, walking barefoot through sandy soil in endemic areas puts the traveler at great risk for developing tungiasis. At the time of infestation, the female jigger is approximately 1 mm in length, but over time (and feeding) grows to the size of a pea.[6] The sand flea lays her eggs within the sinus provided by her human host, and after hatching, the larvae exit the human body via a small aperture that allows the flea to breathe.[6] This aperture remains open for the entire length of her stay, and thus serves as a portal for entry of bacteria that can lead to serious secondary infection. The presence of the flea incites a strong inflammatory reaction and causes intense pain and itching. Complications of tungiasis include tetanus, gas gangrene,[6] and in extreme cases, autoamputation.[7] Recommended treatment is prompt surgical removal of the female flea.[6]

In the patient presented, the location of the lesion is consistent with that of tungiasis. His travel history and punctate nature of the nodule also support a diagnosis of infestation with *Tunga penetrans*. However, there are other features of his nodule that render tungiasis unlikely. First, the diameter of his nodule was outside the range typically reported in tungiasis, which is 5 to 8 mm (Table 1). Second, neither the serosanguineous discharge nor the sensation of

movement reported by the patient are consistent with tungiasis (Table 1). Finally, the pain of tungiasis tends to be more severe and less stabbing in quality, and is maximal at 8 to 12 days post-penetration,[6] features that were not observed in this patient.

Myiasis, the third and final possible cause of this patient's lesion, constitutes an invasion of living, necrotic, or dead tissue by fly larvae, or maggots.[8] There are several species of dipteran flies whose maggots can develop in human flesh. Two main groups of myiasis producing species exist: facultative, and obligate parasites. Maggots of facultative species typically develop in decaying organic matter, but can also survive in animal tissue. Facultative species infest humans when an opportunity, such as a neglected wound, presents itself.[9] Conversely, obligate species must lay their eggs in or on live hosts. Maggots can parasitize the skin, vagina, urinary tract, GI tract, nasopharynx, sinuses, eyes, and auditory canals.[8] The parasite life cycle depends on the method of invasion, but in general, eggs are deposited on skin, wounds, or dead tissue; the larvae then hatch and burrow into adjacent tissue, and emerge after a period of maturation. Maggots do not vector any known diseases, though larvae themselves can cause significant morbidity. The spectrum of disease caused by maggots ranges from mild or asymptomatic infestation to one that is catastrophic.[8] Of particular medical significance are larvae that develop in areas such as the eyes, ears, nose, and throat, where mechanical pressure can lead to severe sequelae.[10]

Cutaneous myiasis can present in four cardinal ways. First, a furuncle or boil-like lesion can develop at a site of trauma or insect bite. The larvae reside in the dermis and cause a painful, pruritic, erythematous nodule that drains serous fluid.[8] The nodule is punctate, and occasionally, the larva may be seen protruding through this aperture.[8] Second, myiasis can present as a 'creeping eruption', in which larvae leave painful erythematous tracks in the skin. This creeping eruption can be distinguished from cutaneous larval migrans (caused by larvae of animal hookworms) because maggots are larger and move more slowly.[8] Third, larvae can invade open wounds and necrotic tissue, leading to secondary bacterial infection. Finally, maggots can mature on the external skin surface, likely within folds where they feed on epidermal debris. This latter type of myiasis is most likely to occur in people with poor personal hygiene or eczematous rashes.[8]

As the lesion in the patient described was a non-migratory subcutaneous nodule occurring on previously healthy skin, myiasis of the furuncular (first) kind is the most likely of the maggot infestations. Two common causal agents of furuncular myiasis are *Cordylobia anthropophaga* (tumbu fly) and *Dermatobia hominis* (human botfly). The tumbu fly has a range restricted to sub-Saharan Africa, whereas *D. hominis* is common from Mexico through the majority of South America.[11] The common presentation of furuncular myiasis is that of a small, raised, red, bite-like lesion that over time evolves to a gradually enlarging, pruritic, erythematous, punctate nodule, from which a sensation of movement and lancinating pain can be

Table 1
Comparison of the Three Common Causes of Fixed, Painful Nodules in Returning Travelers[1,5,6]

	Furuncle (Boil)	Furuncular Myiasis	Tungiasis
Common Etiologic Agents in Humans	*Staphylococcus aureus*	*Dermatobia hominis,* *Cordylobia anthropophaga*	*Tunga penetrans*
Anatomic Location	Neck, face, axillae, buttocks	Exposed areas, face, scalp, trunk, extremities	Around toenails, soles of feet, legs
Predisposing Factors	Obesity Blood dyscrasias Corticosteroid use Neutrophil Dysfunction Diabetes mellitus	Travel to tropics History of insect bite Lack of clothing hygiene	Travel to Central or South America, Africa, India Walking barefoot (esp. near pigsties or cowsheds)
Lesion	Hot, raised, indurated, 1-2 cm	Indurated, erythematous nodule, 1-2 cm	Inflamed nodule, 5-8 mm, central black dot
Punctum	No	Yes	Yes
Pain	++ (painful to touch)	+/- (intermittent, lancinating)	+++ (severe)
Pruritus	No	Yes	Yes
Drainage	Seropurulent	Serosanguineous	Not usually
Sensation of Movement	No	Yes	No
Constitutional Symptoms	Fever, malaise	Generally absent	Generally absent
Treatment	Moist heat Topical antibiotics Oral antibiotics Surgical drainage	Removal of larva Oral antibiotics if cellulitis present	Surgical excision of flea
Complications	Osteomyelitis Endocarditis Metastatic foci	Local tissue reaction Cellulitis Granulomatous inflammation	Tetanus Gangrene Cellulitis

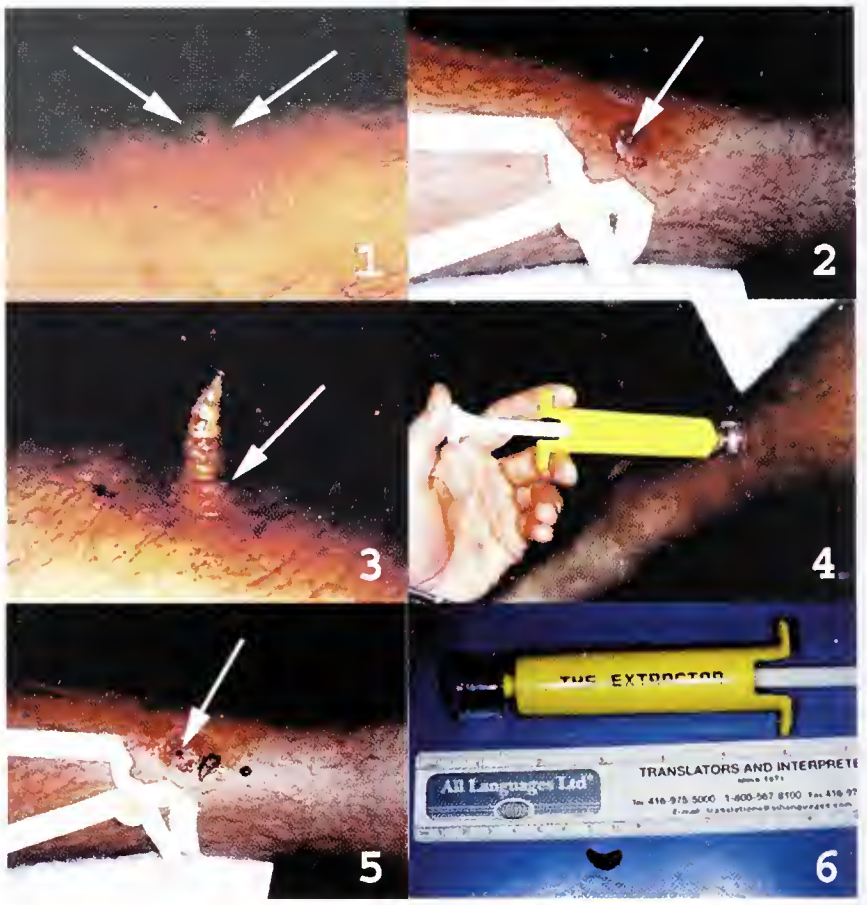
Most patients complain of a serous discharge that issues spontaneously or with application of lateral pressure.[12,24] Constitutional symptoms such as fever, malaise, nausea, arthralgia, and headache are generally absent.[12,24]

Lesions of the tumbu fly are often localized to the trunk, buttocks, and thighs, whereas the botfly has a preference for the scalp, face, forearms and legs,[12] which may reflect its unique life cycle. While *C. anthropophaga* females lay their eggs in urine-soaked soil or dirty clothing left on the ground, the botfly deposits its eggs on the underside of a mosquito, which then serves as a vector for myiasis.[11] Botfly eggs drop off the mosquito as it feeds on an animal (human, bird, other mammal). These then hatch to larvae that are capable of penetrating skin either at the bite wound or elsewhere.[11] Once the botfly larva penetrates skin (after dropping off its vector as an egg), it will remain in the subcutaneous tissue for approximately 100 days. This tidbit of life cycle trivia was elucidated by Busck, who in 1912, voluntarily infested himself in the name of science.[25] After its prolonged stay in the host, the third stage maggot exits via the punctum, falls to the ground, and pupates over the next 2 to 3 weeks.[21,26] At this stage, the maggot may have attained a length of over 2 cm.[26] After pupation, *D. hominis* emerges as an adult, and lives for 8 to 9 days,[21,26] during which time it mates, and pastes it eggs to the abdomens of mosquitoes which will valiantly carry the torch of its life cycle.

As *D. hominis* is a forest dwelling fly, certain occupations and mosquito bites themselves put people at risk of developing myiasis due to the botfly. Conversely, a lack of personal or clothing hygiene are risk factors for contracting tumbu fly myiasis, and drying clothing in bright sunlight is preventive. Conventional treatment of myiasis has focused on removal of the offending maggot. Documented strategies include surgical excision,[10,27] application of lateral pressure,[16,28] and suffocation of the maggot by occlusion of the punctum.[26,29,30] Occlusion of the punctum impairs the ability of the larva to respire, and thus stimulates its migration out of its sinus.[1,26] Materials that have been used to suffocate the maggot include mineral oils,[27] petroleum jelly,[1,26] and pork fat.[29,30] Due to the restricted geographic range of *C. anthropophaga*, it is extremely unlikely that the patient presented in this case was infested with tumbu fly larvae. That he traveled only to Belize makes the human botfly the most likely offender.

Pathological Discussion

The patient returned to the Centre for Travel & Tropical Medicine the following day after wearing the occlusive dressing for 24 hours (Figure 2). On removal of the dressing, the posterior end of what was most certainly a maggot was seen protruding through the punctum (Figures 2 & 3). Although a considerable amount of lateral pressure was applied to the lesion margins, the larva remained partially within the sinus (Figure 3). In the true spirit of scientific inquiry, the attending clinicians then attempted to remove the maggot using a snake venom extractor (Figure 4). Although far less sophisticated than the much-championed oral suction method, in clinical trials this device was actually more efficacious in removing snake venom. Depression of the venom extractor plunger generated a sufficient amount of negative pressure to force the maggot out of its domicile (Figure 5). It is understandable that a significant amount of force would be necessary to extrude the maggot based on its girth relative to the dimensions of the punctum (Figure 5). Careful examination revealed the maggot to be approximately 1.5 cm in length (Figure 6), with a concentric, radial arrangement of black spines. Radial spines allow the maggot to burrow into the flesh like a corkscrew, and anchor itself to prevent premature extraction.[21,31] This burrowing and anchoring is responsible for the lancinating or stabbing pains that patients experience. The skin swab culture indicated a moderate growth of *Staphylococcus aureus*, and heavy growth of group B *Streptococcus*. Based on the patient's travel history and the morphology of the maggot (corpulence, high girth:length ratio, radial spines), a diagnosis of furuncular myiasis secondary to infestation with *D. hominis* was made. Furthermore, the maggot was lovingly reared in the laboratory to an adult stage, and the adult morphology was consistent with that of the botfly.



Figures 1-6. Progression of the patient's lesion over a 24-hour period **1.** The raised, erythematous punctate nodule. Note the arrows demarcating the margins of the lesion. **2.** Appearance of the lesion after 24 hours of occlusion. Note the occlusive dressing and larva occupying the punctum (arrow). **3.** Partially extruded maggot after occlusion. Observe the margins of the aperture (arrow). **4.** Application of the venom extractor. **5.** Appearance of the lesion and maggot post-venom extraction. Note the diameter of the punctum (arrow) relative to that of the maggot. **6.** Scale of the extruded maggot and venom extractor.

Furuncular Myiasis caused by the Human Botfly

Myiasis accounts for roughly 9% of skin lesions in returning travelers.[1] Approximately 10 to 20 cases are seen annually at the Centre for Travel & Tropical Medicine at Toronto General Hospital, and a considerable amount of time has usually elapsed between the onset of symptoms and the time of referral to travel medicine. Myiasis is frequently misdiagnosed as an abscess or furuncle, and subsequently treated with an ineffective course of antibiotics.[13,16,17,22,23] Although the larvae generally require about 12 weeks to mature, most are removed prior to that time. Johnston and Dickinson (1996) offer this explanatory insight: "many inhabitants of the northern temperate regions find the concept of suckling a maturing maggot under their skin for up to 8 weeks aesthetically unappealing if not entirely repugnant".[16]

In the experience of one author (KCK), conventional methods of maggot extraction are often inadequate. Girth and anchoring spines counteract the forces that work to extrude the maggot, and this is why the conventional method of lateral pressure typically fails.

Other therapies such as suffocation necessitate that the patient take the maggot home with them for 24 hours after diagnosis, an experience that might engender some adjustment anxiety. Moreover, suffocation methods that theoretically draw the maggot out of its sinus rarely cause complete extrusion. After partial extrusion, the maggot is often grasped with forceps or some other such device (e.g., fingernails), causing the larva to break and incite an inflammatory reaction that can be severe. And as for the choice of occlusive material, who really wants to keep bacon lying around the office anyway? Surgical excision, while highly effective, is dangerous in that the maggot can be easily lacerated, leading to the same inflammation that results from breakage of the larva during forceps delivery. Surgical excision poses a further risk to patients such as this one who have a concurrent cellulitis as cutting into erythematous, inflamed skin is generally contraindicated.

Using a venom extractor has several advantages over more traditional therapies. First, it is quick, and allows for removal of the larva at the time of diagnosis. It is also less painful than the application of lateral pressure with fingers. Second, it removes the maggot in its entirety, and does not leave behind maggot pieces that result from instrumentation of the cavity or larva itself. Third, venom extractors are completely non-invasive and are therefore safe to use in patients who have a complicating cellulitis, unlike surgical methods. Finally, venom extractors are inexpensive, readily available, and have a much longer shelf life than bacon. Although further documentation of this extraction method will be necessary before it is accepted as an evidence-based practice, venom extraction has the potential to become the treatment of choice for cutaneous myiasis.

Patient Outcome

After extrusion of the maggot, the sinus was irrigated, and the patient was discharged. He continued on his antibiotic regimen until his cellulitis resolved, and the wound left by the maggot healed uneventfully. This case is illustrative of several issues that are becoming increasingly common in travel medicine. First, the actual incidence of myiasis in returning travelers has increased over the last few years[1,16] likely due to the increased accessibility of foreign, exotic travel. Second, that these myiases are often misdiagnosed initially[13,16,17,22,23] allows the portal for entry of bacteria to exist for a longer period of time. In this case, had the original physician made the correct diagnosis, the larva would have been removed at only one week of incubation, and quite likely, the patient would not have developed cellulitis. Additionally, the occurrence of cellulitis should always be considered a serious complication, particularly because of the preponderance of resistant bacterial strains. Prompt initial diagnosis and removal of the maggot can also circumvent complications such as granulomatous inflammation (which can result if the larva dies in the host),[31] or a severe local tissue reaction. In assessing any skin lesion in a returning traveler, it is important to follow the lesion-oriented approach described, and take an exhaustive travel, occupational, and exposure history. Only with this information will the physician be adequately armed to make a correct diagnosis.

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A Suspicious Jaundice

Martin C. Chang, Ph.D. (OT3)
Catherine Chung, B.Sc. (OT3)

Case Presentation

Ken is a 20-year-old, male, community-college student who has been having difficulty at school for the past six months. Describing his tribulations, Ken complained of feeling "wiped out" and nauseous with general aches and pains. When he was able to drag himself out of his dorm room to go to class, he was not able to concentrate and found his hands too stiff to take notes. Over the last few weeks, Ken has noticed that he has been passing darker urine. One week ago, he was brought into emergency after he "seized up" and fell down during his bus ride home.

Ken had not travelled outside of Toronto for two years. He does not smoke, denies using street drugs, and drinks alcohol occasionally (two drinks per week). He had chicken pox when he was six years old, and received all of his childhood immunizations, including hepatitis B, which his mother carries. His medical history was otherwise unremarkable. On examination, Ken was found to be afebrile. In addition, he had yellow-tinged sclera and a tender palpable liver edge. Lab tests were ordered, and Ken was admitted.

Discussion

What is the differential diagnosis for jaundice?

Jaundice is clinically apparent hyperbilirubinemia, and a common sign of liver and biliary diseases. It usually appears when serum bilirubin exceeds 2.5 mg/dL (normal range is 0.5-1.0 mg/dL).[1,2] Most bilirubin is produced in the unconjugated form by the processing of hemoglobin heme groups from senescent erythrocytes. An overproduction of bilirubin, most commonly due to hemolysis, can result in jaundice. Decreased conjugation and hepatic uptake – as occurs with Gilbert's syndrome, Crigler-Najjar syndrome, and drug inhibition – can also cause hyperbilirubinemia (predominately unconjugated bilirubin).[2]

After uptake and conjugation by glucuronyl transferase in the liver, bilirubin is excreted through the bile ducts in its conjugated form. Impaired excretion results in predominately conjugated hyperbilirubinemia, and can result both from hepatic causes (e.g., Dubin-Johnson syndrome, Rotor syndrome, primary biliary cirrhosis, drug-induced cholestasis, septic liver) and post-hepatic causes (e.g., gallstones, neoplastic obstruction, primary sclerosing cholangitis, biliary atresia). Hepatocellular disease (e.g., viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, cirrhosis, Wilson's disease, α_1-antitrypsin deficiency, other metabolic disorders) affects uptake, conjugation, and excretion of bilirubin, and will often result in a mixed-type of hyperbilirubinemia, depending on the etiology and severity.[3,4] Nevertheless, bilirubin excretion is the rate-limiting step, and predominately conjugated hyperbilirubinemia will underlie jaundice due to hepatocellular disease.[5]

What are the neurological complications of liver disease?

Hepatic encephalopathy can result from both acute liver failure and chronic liver disease. The acute form is associated with fulminant liver failure, and presents as cerebral edema and coma. Chronic liver disease is thought to result in the shunting of nitrogenous and other neurotoxic compounds to the systemic circulation. Some of these compounds may act as "false neurotransmitters" and disrupt cerebral function. Consequences include cognitive loss, asterixis, movement disorders (including parkinsonism), hyperreflexia, and coma.[2]

Case Presentation

Both blood tests and a liver biopsy were ordered. Within two days, the report from the laboratory was available, and is presented as Table 1. The biopsy report was available several days later, and showed fatty changes, ballooning hepatocytes with multiple vacuolated nuclei. No cirrhotic changes were evident. A sample section is shown in Figure 1.

Discussion

What is the diagnostic significance of the lab results presented so far?

The initial clinical presentation raises the suspicion that Ken has chronic hepatitis, possibly of viral origin. The lab results in the left half of Table 1 are consistent with mild-to-moderate hepatocellular inflammation. This commonly leads to a greater elevation in aminotransferase activities compared to ALP, GGT and 5'-NT activities, which are more highly elevated in cases of biliary obstruction.[4] The high (>50%; 20% normal) fraction of conjugated bilirubin normally occurs with biliary obstruction; however, it is also consistent with hepatocellular damage. Although enzymatic conjugation of bilirubin is often compromised by severe hepatocellular inflammation and necrosis, the excretion of conjugated bilirubin is usually the rate-limiting step. The accumulated conju-

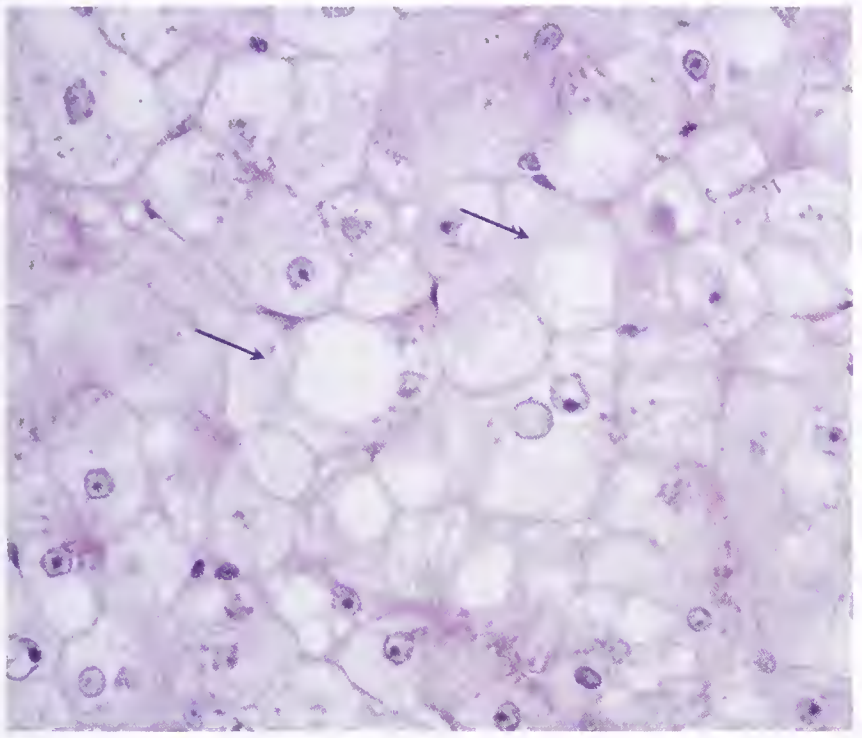

Figure 1. Liver biopsy section of mild hepatitic inflammation due to Wilson's disease. H&E stain 150X. Examples of balloon-hepatocytes with vacuolated nulcei are indicated by arrows. (Provided by Dr. I. Wanless, Department of Pathology, Toronto General Hospital, University Health Network.)

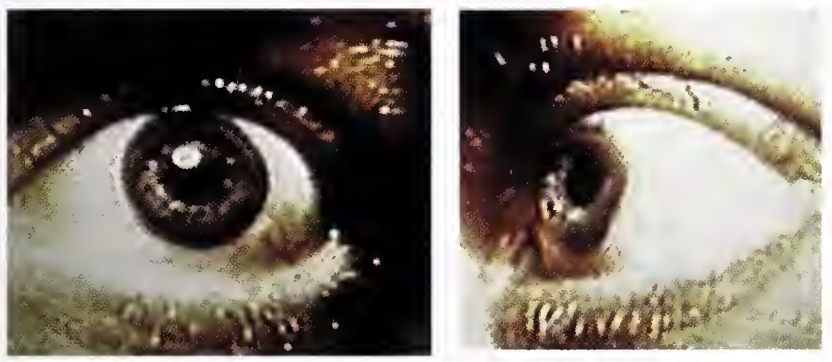

Figure 2. Kayser-Fleischer rings in a patient with Wilson's disease. (Source: Michigan State University, College of Human Medicine)

gated bilirubin will therefore enter the circulation (instead of the bile), and also the urine, in which it is visible as a dark pigment. The biopsy results confirm inflammatory changes, and show a mild-to-moderate histological severity without widespread fibrosis. These results do not, however, definitively provide a clear etiology.

The two most common causes of hepatocellular disease are viral infection and chronic alcohol abuse.[2] Ken's alcohol intake seems insufficient to cause alcoholic hepatitis. It is unlikely that Ken has under-reported his alcohol consumption, in which case the serum GGT level would probably have been elevated to a much higher degree. Moreover, the lab results presented in the right half of Table 1 seem inconsistent with a viral cause for Ken's hepatitis. Ken has been immunized for the hepatitis B virus, and no active HBV or HCV antigen was found in his blood. Hepatitis A presents more acutely, with a 4-week incubation period, and without a significant travel history other viral causes are unlikely. As hepatocellular inflammation has been established without a definitive cause, further prompt investigation is indicated.

What should we now suspect, and how might these suspicions be tested?

The routine work-up shown in Table 1 is not sufficient to identify a number conditions that underlie hepatocellular disease, e.g., metabolic disturbances and autoimmune disease. The most important consideration for a young person presenting with both hepatic and neurological symptoms is Wilson's disease (see next section). If suspected, Wilson's disease is easily confirmed by measuring serum copper, ceruloplasmin, and urine copper. A classic physical finding of Wilson's disease is the Kayser-Fleischer ring: greenish-brown marks at the periphery of the cornea (Figure 2) that may not be visible until the later stages of the disease.[6] Slit-lamp examination is often necessary to see the rings clearly.[2]

Autoimmune hepatitis is a condition with a variable presentation and unclear pathogenesis. It is often associated with other pre-existing autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, glomerulonephritis, juvenile diabetes, etc.[3] Laboratory values that may distinguish autoimmune from other causes include autoimmune antibodies such as anti-nuclear antibody (ANA), rheumatoid factor (RF), and smooth-muscle antibodies (less specific), in addition to antibodies against liver proteins, such as anti-liver/kidney microsomal antibody (anti-LKM). Nevertheless, these autoantibodies are not established causes of hepatocellular damage, and a diagnosis of autoimmune hepatitis remains a diagnosis of exclusion.

Case Presentation

Ken was worked up specifically for Wilson's disease. The serum ceruloplasmin was found to be 12 mg/dl (24-46), the serum copper 60 mg/dl (70-100), and urine copper 500 µg/24 h (15-60). A regimen of *D*-penicillamine, 1 g daily, with a 25 mg pyridoxine supplement, was ordered immediately. Ken remained in hospital with regular checks of leukocytes and platelets, to ensure tolerance to penicillamine. Penicillamine copper-chelation, along with a copper-reduced diet, will be continued throughout Ken's life with regular monitoring of liver function, serum and tissue copper levels, neurological signs, and drug toxicity.

Discussion

What is the etiology and natural history of Wilson's disease?

Very small amounts of copper are necessary for normal physiological function. The average diet contains copper far in excess of need, and the absorption of dietary copper is not as tightly controlled as that of iron. As a result, copper balance in the body must be highly regulated, allowing only trace amounts to be present at any given time. Most of the body's copper is stored in the liver, and transported in the plasma by the binding-protein ceruloplasmin. Wilson's disease arises from any of a number of mutations of the ATP7B gene on chromosome 13, coding for a copper-transporting ATPase.[2,4,6] The precise mechanism of action of this protein remains unclear; however the mutations have been shown to reduce both copper excre-

Table 1
A "Routine" Work-Up

Test	Result	Normal	Test	Result	Normal
Bilirubin	2.6 mg/dL	0.3-1.0 mg/dL	Hb	130 g/L	138-172 g/L
	>50% conj.	<20% conj.	WBC	6.3 x 10^9/L	3.8-10.8 x 10^9/L
AST	620 U/L	<42 U/L	Plt	98 x 10^9/L	130-400 x 10^9/L
ALT	550 U/L	<47 U/L			
GGT	85 U/L	45-65 U/L	HBsAb	pos	
ALP	118 U/L	<125 U/L	HBsAg	neg	
5'-NT	16 IU/L	2-16 IU/L	HBeAb	neg	
			HBeAg	neg	
PT	14 s	10-12.5 s	Anti-HCV	neg	
Albumin	3.6 g/dL	3.5-5.0 g/dL	Creatinine	1.0 mg/dL	0.6-1.2 mg/dL
			BUN	14 mg/dL	8-18 mg/dL

tion and ceruloplasmin activity (possibly as a secondary effect). As a result, copper accumulates in the liver, damaging hepatocytes and eventually releasing excess copper ions into the blood and tissues.

Wilson's disease usually presents between the ages of 5 and 30.[2] It manifests itself as any combination of hepatic (e.g., jaundice, hepatitis, cirrhosis, portal hypertension, encephalopathy), neurological (e.g., parkinsonism, chorea, dystonia, rigidity; sensory neurons are usually spared), psychiatric (e.g., mood disorders, behavior disorders, schizophrenia, dementia), and hematological (e.g., intravascular hemolytic anemia) signs.[4] Patients with Wilson's disease can also present with osteoarthropathies, spinal deformities, gallstones, and secondary hypoparathyroidism. Occasionally, an asymptomatic patient is diagnosed based on either family history or incidental laboratory testing. Such a patient, if untreated, will eventually become symptomatic. Symptomatic patients, if untreated, will accumulate copper in the liver, brain, and other tissues, eventually suffering frank end-organ damage.

Copper-chelation therapy stops further damage and allows the natural resolution of reversible damage. Irreversible damage in cases of severe disease, particularly liver cirrhosis and brain damage, will persist and require further treatment, such as liver transplant and supportive therapy for mental illness. Cessation of therapy is certain to cause recurrence of the disease and can be fatal.[6]

Acknowledgements

The authors wish to thank Dr. Wayne Gold for reviewing this article and Dr. Ian Wanless for providing the pathology slide of a Wilson's disease liver.

Clinical Pearls

- Wilson's disease, a defect in copper storage, is a rare hereditary condition that is easily diagnosed and treated if suspected.
- Sometimes, physicians may not suspect Wilson's disease, due to its protean presentation.
- A young person (5-30 years old) presenting with liver disease, with or without neuropsychiatric symptoms, should always be worked-up for Wilson's disease.

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Case Reports from the University of Toronto Faculty of Medicine

Piero Tartaro, B.Sc. (0T3)
Steven W.H. Hwang, B.Sc. (0T3)
Shoba Subramanian, B.Sc. (0T3)

Case 1

Dr. Joel G. DeKoven, M.D., MHSc., FRCP(C)
Sunnybrook and Women's College Health Sciences Centre
Division of Dermatology, Department of Medicine

A 47-year-old man presented to the dermatologist with various lesions on his body. On examination, he had multiple erythematous plaques and depressed scars on his chest and arms. On his anterior thighs, scattered small erythematous papules intermingled with large ulcerations with heaped up borders and undermined edges were noted (Figures 1.1 & 1.2). The patient had also developed an arthritis of various joints which seemed to be associated with a small canker sore and gingival infection. Otherwise, the patient was healthy and had no significant past medical history.

What is the likely diagnosis?

Figure 1.1. Lesion on patient's arm

Figure 1.2. Lesion on patient's thigh

Case 2

Sonya M. Cook (0T2), M.Sc.
University of Toronto, Faculty of Medicine

A 34-year-old G2P2 woman presented to the emergency room complaining of a severe headache which had persisted for three days. Associated symptoms included nausea, decreased appetite and increased fatigue. The history revealed that she had been well until one month earlier, when she began to experience severe headaches with increased frequency. She reported regular menses and a last menstrual period of 1 month prior to her presentation. Her most recent pregnancy was four years ago. She was not taking any medications. On examination, blood pressure was 114/67, heart rate was 81 beats/min, and she was afebrile. The patient was alert and oriented, with no visual disturbances or focal neurological signs. The remainder of the physical exam was unremarkable. Past medical history and family history were noncontributory. Laboratory tests were performed and the serum beta-hCG value was 166,953. Pelvic ultrasound revealed a hypervascular, echogenic focus continuous with the endometrium. MRI of the head showed a 9 mm lesion in the right frontal cortex of the brain consistent with a metastasis (Figure 2). CT scanning of the thorax, abdomen, and pelvis revealed a single metastatic lesion in the head of the pancreas and multiple metastases within the liver and lungs.

What is the diagnosis?

Figure 2. MRI of brain

Case 3

Robert T. Hillard, M.D., EdD, FRCPC
Division of Pediatric Medicine, The Hospital for Sick Children

A 14-year-old girl was admitted to the hospital with a four week history of fatigue, pallor, loose bowel movements with bright red blood in her stool and periorbital edema. Except for an episode of gastroenteritis at six months of age, she had been in good health with normal development. She had lost 3 kg over the past 4 weeks and presently weighed 43 kg. Physical examination confirmed edema, ascites, and features of a left pleural effusion. Abdominal palpation revealed no organomegaly.

Chest x-rays are shown below. (Figures 3.1 and 3.2)

Laboratory examinations:
Hb 58 g/L with a microcytic hypochromic smear
Ferritin 13.6 µg/L
WBC 7.5 with a marked lymphopenia
Albumin 16 g/L
Urinalysis – normal
Liver function tests – normal

What are possible diagnoses to explain this clinical picture and what investigations are indicated?

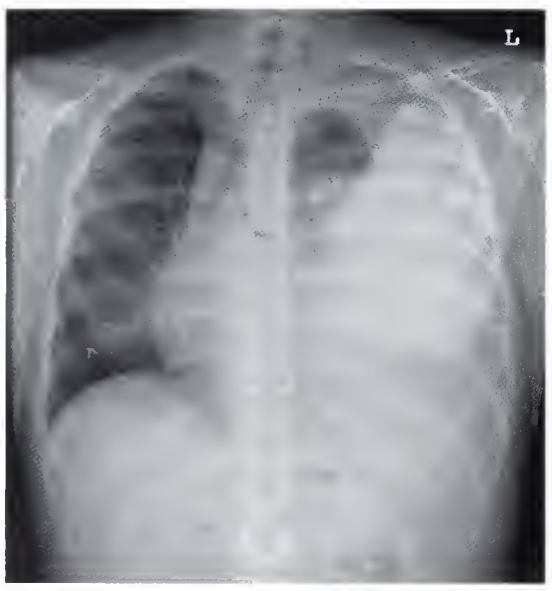

Figure 3.1. PA chest x-ray

Figure 3.2. Lateral chest x-ray

Case 4

Dr. Erik L. Yeo, M.D., F.R.C.P.(C)
Division of Hematology, Department of Medicine
University Health Network

A 25-year-old women, 5 months postpartum, presented with hip pain after having fallen on her left hip. On further inquiry, she reported having difficulty adducting her left leg and movement of that leg was painful. In addition, she reported spontaneous bruising during the prior two to three weeks. CT of the abdomen revealed a significant left ileopsoas muscle hematoma. She was otherwise well, had no past history or family history of bleeding disorders, was on no medications, and had no significant past medical history. The platelets, prothrombin time, and thrombin time were normal. CBC revealed an anemia, the partial thromboplastin time was prolonged at 60 seconds, and the fibrinogen was increased.

What is the most likely diagnosis?

Case 5

Dr. Fahad Al-Mukhaizeem MB Bch FRCP(C) FAAP
Fellow in Pediatric Emergency Medicine, Hospital for Sick Children
Dr. Luba Komar MD FRCP(C) FAAP
Assistant Prof of Pediatrics Division of Emergency Medicine, Hospital for Sick Children

A healthy 13-year-old girl was brought to the Emergency Department (ED) for assessment of a recurrent lump on her forehead. She had no significant past medical history, and had received only one immunization at 6 months of age. Two weeks prior to her assessment in the ED, she had hit her head during sleep, but having had no symptoms was not evaluated at that time. Two days later she developed a swelling over the dorsum of her nose and over her left eyebrow. Being active in sports, she proceeded with her scheduled swimming and diving despite the swelling. She saw her G.P., who advised her to treat the swelling with ice, and after a few days the lump subsided. Five days prior to ED assessment, she again went swimming and diving (in an indoor pool, with goggles) and 2 days later developed the left sided forehead swelling once again. In the ED, she complained of itchiness and tightness of the lump, and of one transient episode of blurred vision. There was no history of fever, erythema, rhinnorhea, CSF leak, headache or any other neurological or constitutional symptoms. On examination, the girl appeared well and was afebrile (although a recheck of her temperature revealed a temperature of 38.9°C). She had a very significant warm, erythematous, soft, slightly tender, ovoid, fluctuant protuberance (approximately 3 x 3 x 2 cm) of the forehead over her left eye. The remainder of her physical exam was totally unremarkable. The diagnostic investigations, including a skull x-ray (Fig 5.1) and a CT Head with contrast (Figures 5.2 and 5.3) are shown below.

1. What is the differential diagnosis of the supraorbital swelling shown in Fig 5.1?

2. What is the diagnosis on the basis of the CT scans (Fig 5.2 & 5.3)?

3. How would you manage this child?

Figure 5.1.

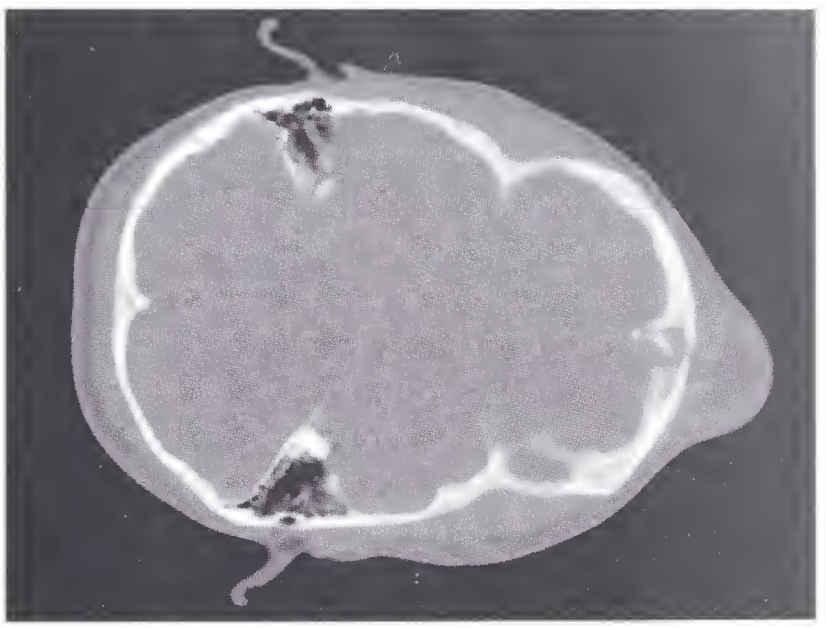

Figure 5.2.

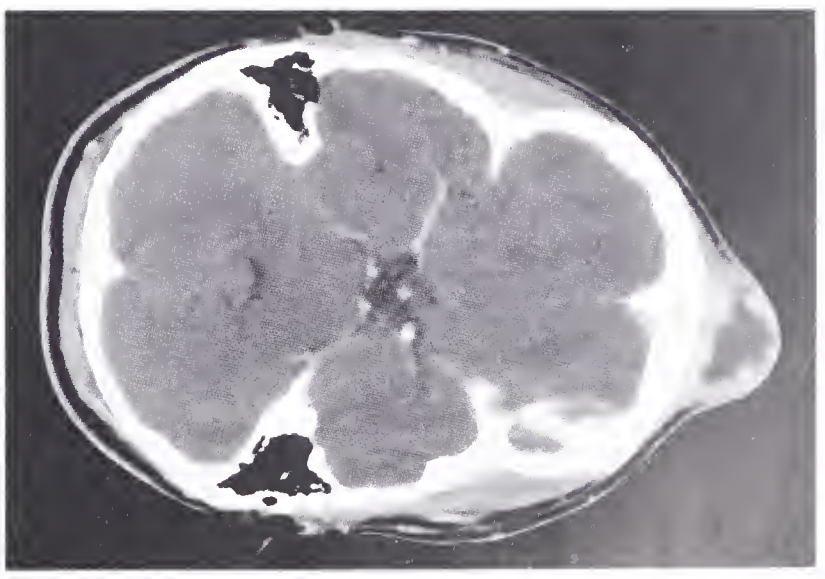

Figure 5.3.

Case 6

Kevin [illegible] MD, FRCP(C)
[illegible] Infectious Diseases and Tropical Medicine, University Health Network

A 44-year-old woman experienced symptoms of nausea and generalized fatigue for 3 weeks following her return from travels in Kenya and Tanzania of 3.5 weeks. Three weeks following her return, she began spiking recurrent fevers of 40°C daily, and was assessed in the ER. Physical exam revealed mild diffuse erythema involving her legs and back and an innocuous looking abrasion on her big toe, which the patient attributed to her new sandals. Complete blood count and liver function tests were normal (Figures 6.1 and 6.2). Blood cultures and films were taken to rule out malaria. The woman was sent home. The next day, the patient developed severe watery diarrhea and vomiting and was reassessed. She was hypotensive with a systolic blood pressure of 90 mmHg. She was treated with ciprofloxacin for a presumed enteric infection caused by Campylobacter. The following day, the patient experienced desquamation of her hands. A swab of her foot lesion was taken for culture and sensitivity.

What is the diagnosis?
How should the patient be managed?

Figure 6.1. Mild diffuse erythema of the back

Figure 6.2. Innocuous abrasion on the left big toe

Case 7

Robert I. Hilliard, M.D., EdD, FRCPC
Division of Pediatric Medicine, The Hospital for Sick Children

A 9-1/2 month old girl was seen for poor weight gain and recurrent illnesses. She had previously been admitted to a local community hospital for up to 3 weeks because of gastroenteritis and dehydration on one occasion and for poor weight gain on four other occasions. Some feeding difficulty along with recurrent vomiting was reported as well as one episode of diarrhea with no history of cough or other infection. The child's birth weight was 2.95 kg and her height was 43.2 cm. At presentation, her weight was 6.3 kg and her height was 64.5 cm. Her growth charts are included on the next page.
Her mother is 20 years old and single with a healthy two-year old daughter. The mother has a history of chronic psoriasis and may have been on methotrexate during her pregnancy. She has also had an unknown number of spontaneous abortions. Because of the "failure to thrive" (Figure 7.1 and 7.2), the recurrent hospitalizations and because the mother seemed "stressed out", a public health nurse had been visiting the home and the Children's Aid Society had been involved with the family.

On examination, the child was small but did not seem malnourished. Her general exam was unremarkable, her development seemed normal, but she had puffy, swollen feet.

What might be the explanation for her poor growth?
What investigations are indicated?

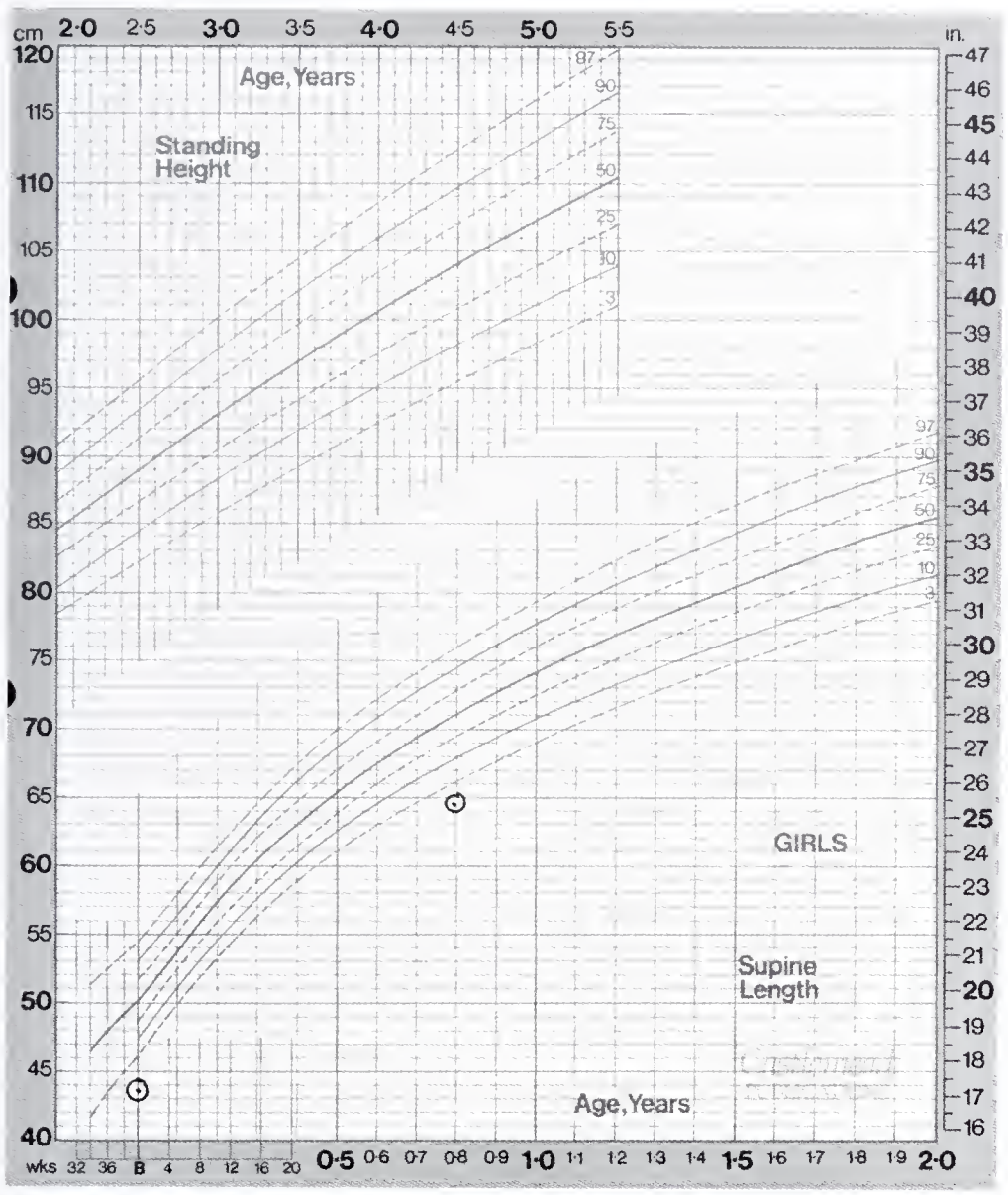

Figure 7.1. Height chart

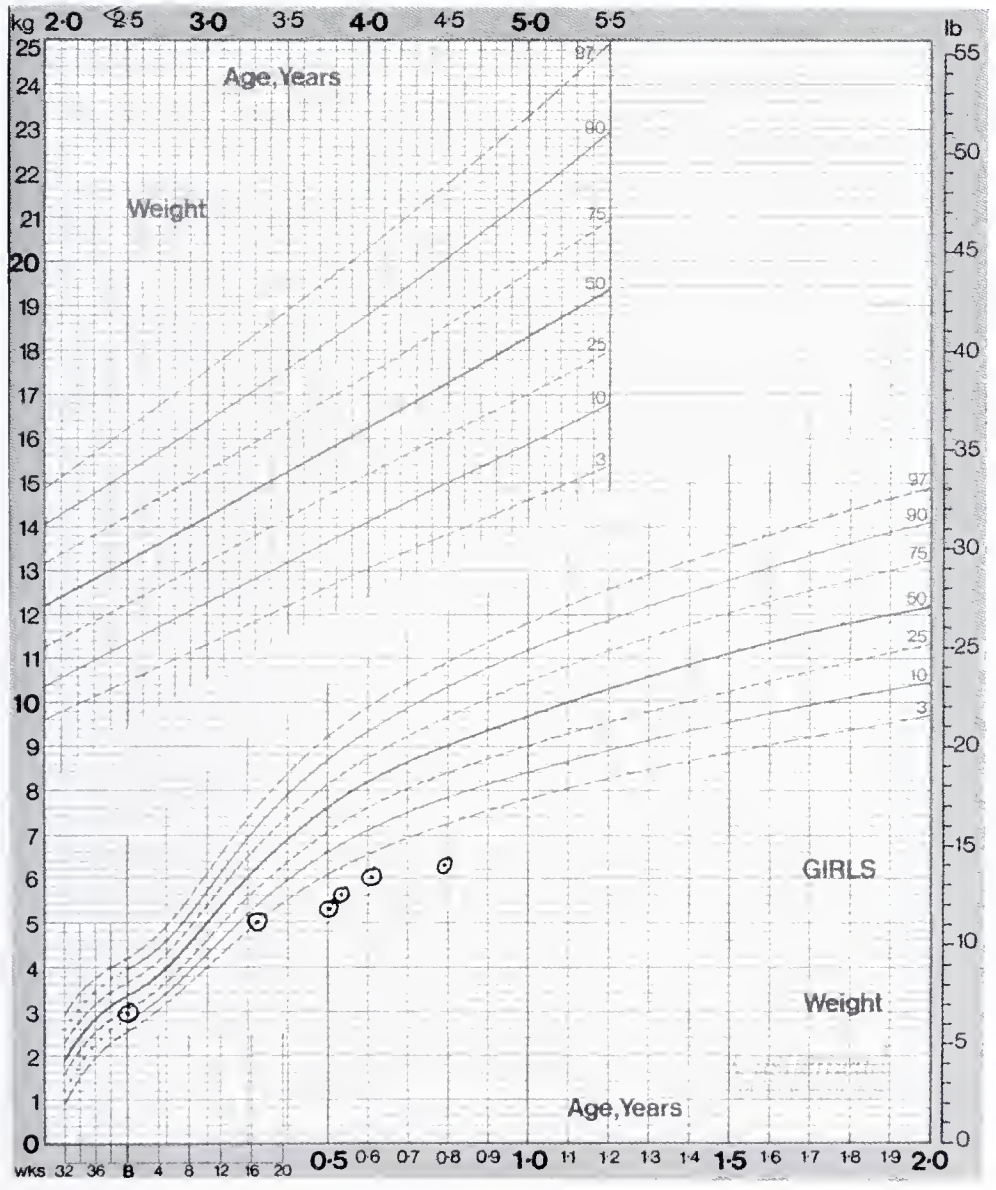

Figure 7.2. Weight chart

And the diagnosis is...

Case 1

Diagnosis: Pyoderma gangrenosum

The cutaneous manifestations described are indicative of pyoderma gangrenosum (PG), a poorly understood ulcerating skin disease. Diagnosis is usually made on clinical appearance since biopsy and laboratory testing has little diagnostic value. In 20% of patients, the disease is characterized by pathergy, a phenomenon in which minor trauma, even from venipuncture can provoke new lesions or aggravate existing ones. PG often occurs in patients with chronic underlying inflammatory or malignant disease such as ulcerative colitis, rheumatoid arthritis, chronic active hepatitis, Crohn's disease, IgA monoclonal gammopathy, and hematologic and lymphoreticular malignancies. However, in 40-50% of cases no associated disease is found.

This patient has had no history of genital lesions, neurological complaints or ocular problems, and aside from the solitary minor aphthous sore (that may have been related to a dental problem) he had no other oral lesions. A complete workup for the underlying etiologies of PG, including inflammatory bowel disease and rheumatoid arthritis, was negative.

The patient was put on prednisone and potent topical corticosteroids that resolved the lesions. However, since his first presentation 9 years ago, the patient has had multiple recurrences of PG that typically have developed following the discontinuation of the prednisone. Currently, he is on dapsone and alternate day prednisone, as well as Tegaderm™ for local treatment. Due to the long-term use of prednisone (and its potential side-effects), he is currently on etidronate (Didronel™) and vitamin D, has regular bone densitometries, and is being seen by an ophthalmologist.

Case 2

Diagnosis: Choriocarcinoma with metastasis to the brain, lungs, liver, and pancreas

Chorionic tumours, or gestational trophoblastic diseases, originate from placental tissues. Gestational trophoblastic disease refers to a spectrum of pregnancy-related trophoblastic proliferative abnormalities, including partial and complete hydatidiform mole, placental-site trophoblastic tumour, and choriocarcinoma, that vary in their propensity for local invasion and metastasis. In chorioearcinoma, the predisposition of normal trophoblast to invasive growth and erosion of blood vessels is greatly exaggerated. Metastases often develop early and are usually blood-borne due to the affinity of trophoblast for blood vessels. The most common sites of metastasis are the lungs, vagina, liver, and brain. As demonstrated in this case, some patients with extensive systemic involvement have minimal or no gynecologic symptoms (the most common being abnormal vaginal bleeding). This patient was diagnosed with stage IV disease (indicating hepatic or cerebral involvement) and combination chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine was initiated. The patient also received adjuvant radiation to prevent intracranial hemorrhaging. Chemotherapy was administered until human chorionic gonadotropin levels were undetectable, at which time additional chemotherapy was given to reduce the risk of relapse. Choriocarcinoma is now curable in most cases.

Case 3

Diagnosis: Primary intestinal and thoracic lymphangiectasis

Pleural effusions may be considered as exudates or transudates, and are commonly due to infection, malignancy or are associated with hypoproteinemia. In this case, there was no fever or other suggestions of an infection, pneumonia or tuberculosis and an extensive work-up was done to look for a malignancy. A CT scan showed the pleural effusion and an abnormal signal in the mediastinum, but a bone marrow and thoracoscopic biopsy of her mediastinum were negative for any lymphadenopathy or malignancy. However, not only was there a pleural effusion but there was also evidence of a protein-losing enteropathy and an endoscopy eventually showed features of an intestinal lymphangiectasis (often small bowel wall thickening is observed).

The thoracic lymphangiectasia accounts for the large pleural effusion while the intestinal lymphangiectasia accounts for the hypoproteinemia (protein losing enteropathy), lymphopenia and hypogammaglobulinemia.

Case 4

Diagnosis: Acquired hemophilia

This history is compatible with an acquired bleeding disorder. Further laboratory tests revealed a reduced factor VIII level and the presence of factor VIII inhibitory activity, confirming a diagnosis of acquired hemophilia. Acquired hemophilia is a rare condition with a prevalence of approximately one in 1-4 million. It is caused by autoantibodies to factor VIII which deplete circulating factor VIII. It has been associated with various autoimmune diseases, lymphoproliferative malignancy, drug reactions, and, as in this case, pregnancy (commonly occurring 2-5 months postpartum). However, in most cases there is no known association.

Autoantibodies to all clotting factors have been described, but those directed against factor VIII are by far the most common. The diagnosis is usually suggested, as in this case, by the spontaneous onset of severe bruising and hemorrhage in a patient with no previous bleeding history. The objectives of treatment are to eliminate the inhibitor with immunosuppression and to treat the hemorrhagic complications. This patient was put on prednisone and cyclophosphamide, and was give porcine factor VIII to restore her clotting ability. The porcine factor VIII has very little or no cross-reactivity so it is effective in treatment.

The patient's course was complicated by a left femoral nerve palsy secondary to the hematoma which resulted in persistent neuropathic pain necessitating gabapentin and dilaudid for pain control. She will most likely remain on immunosuppressives until the factor VIII levels return to normal. Most acquired hemophiliacs return to normal and never have a recurrence of the condition.

Case 5

Diagnosis: Pott's puffy tumour

The skull X-ray shows significant soft tissue swelling over the frontal bone without any bony destruction. The differential diagnosis of unilateral periorbital/supraorbital swelling is quite wide and includes: frontal sinus abscess, periorbital and orbital cellulitis, Chagas disease (Romana's sign is a unilateral firm edema of the eyelid and is the earliest indication of infection), Trichinosis, Graves' opthalmopathy, dermatomyositis, allergic reactions including exercise-induced anaphylaxis, and blepharochalosis (redundant fold of the upper eyelid).

Figures 5.2 and 5.3 demonstrate the destruction of both the inner and outer bony tables of the frontal bone, the opacification of the left frontal sinus, and the periosteal abscess. The diagnosis is Pott's puffy tumour, a spreading frontal bone osteomyelitis with a periosteal abscess and overlying soft tissue swelling which is a complication of frontal sinusitis. Although rare in the post antibiotic era, it most commonly occurs in older children and adolescents. Other frontal sinus complications include orbital complications: periorbital/orbital cellulitis, subperiosteal/orbital abscess, and cavernous sinus thrombosis. Potential intracranial complications beeause of both direct extension and hematogenous spread include subdural empyema (most common), frontal lobe abscess, cerebral abscess and epidural abscesses. Commonly isolated infectious agents include streptococci, staphylococci, oral anaerobes, and rarely, gram-negative bacteria.

Due to the serious risk of suppurative CNS complications, aggressive management is necessary and includes both surgical drainage and debridement (usually requiring a combined neurosurgical and ENT team). In addition, the patient will be started on high-dose IV antibiotic therapy for 6 weeks with antibiotics that penetrate into the CNS and have broad streptococcal, staphylococcal and oral anaerobic coverage until culture-directed IV antibiotic therapy based on both aerobic and anaerobic culture from the patient can be instituted. This patient had a frontal craniectomy, debridement of epidural granulation tissue, removal of the left frontal sinus mucosa and drainage of the left maxillary sinus followed by 6 weeks of culture-directed IV antibiotics. Several organisms were isolated including 2 strains of *Streptococcus viridans, Streptococcus anginosis*, coagulase-negative *Staphylococcus*. and *Propionobacterium acnes*.

Case 6

Diagnosis: Toxic Shock Syndrome Related to Nonmenstrual *S. Aureus* Infection

The swab of the foot lesion demonstrated staphyloccocal and streptoccocal infection, which supported the diagnosis of nonmenstrual toxic shock syndrome. Toxic shock syndrome (TSS) is an acute multisystem disorder, characterized by fever, hypotension, erythematous rash, desquamation of the skin associated with recovery (1-2 weeks after the onset of illness), and variable multiorgan involvement. Erythema of conjunctivae and mucous membranes of the tongue, mouth, vagina, and tympanic membrane is common. Staphylococcal TSS can be divided into menstruation associated cases, related to tampon use, and nonmenstrual cases. Nonmenstrual cases of TSS are associated with skin and soft tissue infections, superinfections of existing skin lesions caused by varicella zoster virus and burns, primary staphylococcal soft tissue infections, and surgery. TSS toxin-1, produced by certain strains of *S. aureus* is the cause of nearly all menstrual cases and approximately 50% of nonmenstrual cases. The majority of streptococcal TSS is caused by Group A Streptoccoccal strains (*S. pyogenes*). The clinical presentation and isolation of toxin producing *S. aureus* or *S. pyogenes* from a nonsterile site (e.g., throat, sputum, vagina, superficial skin lesion, or wound), or a normally sterile body site, is the most definite way to make the diagnosis of TSS.

The patient's hypovolemia was corrected and anti-staphylococcal and anti-streptococcal therapy was initiated with cephazolin™.

Case 7

Diagnosis: Turner Syndrome

Edema of the feet may be caused by many disorders such as hypoprotcinemia (on the basis of poor protein intake, malabsorption, protein loss or nephrotic syndrome) cardiac, liver or renal disease. However, peripheral edema in the feet may be seen with primary lymphedema, and lymphedema in the newborn period is not an uncommon feature of Turner syndrome. Turner syndrome occurs in about 1/4000 female live births, but represents about 3% of fertilizations (99% are aborted). A chromosome study showed the typical karyotype 45X of Turner syndrome.

Individuals with Turner syndrome have an increased risk for heart and kidney malformations and thus a cardiac, renal, and ovarian ultrasound investigation is warranted. Often, a webbed neck can also be seen on inspection and may help guide the diagnosis. Although there was a difficult social history, the child was both short and underweight and her weight was appropriate for her height. This symmetric poor growth is more in keeping with a primordial or genetic cause for her small size rather than non-organic failure to thrive.

Handheld Computers and Medicine: A Brief Review of Hardware and Software Options

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Introduction

Handheld computers, or "personal digital assistants" (PDAs), are increasingly being used by our peers in medicine. For example, Wake Forest University School of Medicine recently began to provide second- through fourth-year students, who spend more time in direct patient care, with a handheld device to carry with them on their rounds.[1]

A survey at a national meeting of the American Medical Students Association indicated that 22% of respondent medical students used handheld computers. When the remaining 78% were questioned about their attitudes toward "handhelds", an overwhelming majority believed them to be very useful for both personal and professional data management. Three-quarters of current non-users reported plans to buy a handheld computer within the next year. Although this survey was conducted by MedCompanion Inc., a company that offers clinical handheld computing solutions to physicians, and thus may not be free of bias, the results seem to clearly demonstrate the receptivity of students to emerging technological aids.

Of those using handhelds, the survey found that:

- 63% use condensed versions of medical textbooks;
- 38% use prescription drug references;
- 20% use a patient tracking program;
- 13% use procedure logs.[2]

In fact, Palm, Inc. lists Toronto's own Mount Sinai Hospital as one of the organizations that are employing Palm Operating System (OS) technology.[3] Cedars-Sinai Medical Center in Los Angeles and Harvard Medical School are among a growing list of medical teaching institutions and care centres that are using handheld computers.[4]

Cedars-Sinai Medical Center uses the Palm VII, which has wireless capabilities, to provide clinicians with access to a physician directory, paging, and e-mail, in addition to secure access to confidential patient information, and wireless order-processing for books and articles from the medical library.[5]

Given the vast array of models to choose from, how does one go about assessing and finally choosing a handheld device? There are many models of handhelds, some of which will be briefly discussed in this article. Factors to consider include functionality, price, and expandability. The functionality inherent in handhelds has played a key role in their success. The convenience of carrying out tasks such as scheduling, jotting down quick "to-do" lists and looking up phone numbers have made portable devices popular to a diverse population of users. Given the vast information content of medicine, and the fact that handhelds are able to store medical texts and drug databases, handhelds have become popular among medical students and staff. The on-line accessibility of wireless devices, many of which are expected to emerge soon, have made handhelds popular to organizations and medical centres like that at Cedars-Sinai Medical Centre for the reasons listed above. Price is always an issue, especially for the student buyer. This is also a market where the technology is developing very rapidly, with better and smaller devices always on the horizon. At the time of this writing, two high-end devices employing new technology, the Visor Edge™ and Palm m500™ series, are new to the market. Currently, the majority of models use 8 MB of RAM (random access memory). This amount of memory provides enough room for a good pharmacopoeia such as *ePocrates qRx* and one large reference book, such as the *Merck Manual*, or two smaller texts such as *Harrison's Companion Edition* and the *5-Minute Clinical Consult*. Some users want it all, and thus expandability, specifically in terms of memory upgrades, is an important consideration.

The focus of this article is on the Palm Operating System (OS), which dominates the handheld market. Other available operating systems include PocketPC/WindowsCE, EPOC and Linux, which collectively make up about 15% of the North American handheld market. PocketPC, the current Microsoft handheld operating system, makes up the bulk of this non-PalmOS market. On the hardware side, *PC Data* reports that in January 2001, Palm, Inc. branded hardware accounted for 60.5% of handheld models sold, while Handspring, who also uses the PalmOS in their Visor devices, holds 26.2% of the market.[6] These two dominant companies have currently added new models to their line-ups, the success of which will be interesting for investors to follow.

Low-to Mid-Range Hardware

Palm's lower-end offerings inelude the m100™ and m105™. The m100 comes standard with a 16-MHz processor, 2 MB of non-upgradeable memory, and a smaller screen than the other Palm handhelds. The m105 is similar, but eomes with 8 MB of on-board memory and a Mobile Internet Kit, whieh ean be used with a modem or cell phone to wirelessly access e-mail or web information from any location. Both also allow the user to ehange the faeeplate of the device to suit his or her own partieular style.[7] These devices are poised to replace the Palm III series, whieh is currently being discounted by Palm. The eolour-sereened Palm IIIc™ will likely be supplanted by the high-end m505 discussed below.

Handspring released the Visor, its flagship product, in 1999. Sinee that time, the Visor's attraetive features, such as modular expandability and lower price, have enabled Handspring to capture about 25% of the entire handheld market. This was achieved in spite of the faet that the version of the PalmOS that Handspring includes on their devices cannot be upgraded, unlike units produeed by Palm, Sony, IBM, and TRG. The Visor Deluxe™, for instanee, ships with OS 3.1 and a 16-MHz proeessor, whereas the Visor Platinum™, Edge™, and Prism™ all ship with OS 3.5.2 and come with a 33-MHz Motorola Dragonball processor.[8] Whether using devices without an upgradeable OS will be a problem or nor will depend on the software and add-on hardware that an individual wishes to use. Most software today does not require operating software greater than OS 3.1. Whether this will remain the case is far from eertain, espeeially eonsidering that Palm is set to release PalmOS 4.0 in March 2001, and OS 5.0 is scheduled to debut in 2002.

In the past year, however, Handspring has garnered substantial third-party support for their proprietary "Springboard™" expansion slot. This slot permits the use of add-on modules. There are now quite a variety of add-on devices for the Visor, among which are global positioning system (GPS) units, digital cameras, MP3 players, and modems. In addition to these add-ons, Margi Systems has released the Presenter-to-Go™ Springboard module which permits the user to run a PowerPoint™ or web-page presentation from a handheld. This function may even be controlled remotely via the IR (infra-red) port.[9] To follow suit, the new Palm m500 series will also have expansion capabilities via Seeure Digital teehnology, diseussed below.

Among the smaller players in the PalmOS market are TRG and Sony. TRG devices use CompactFlash™ (CF) expansion slots,[10] which may be advantageous sinee CompactFlash has become a standard in solid-state memory and expansion units for other equipment, such as digital cameras. Other plug-ins produced for the CF slots include modems and wireless conneetivity deviees. A current list of sueh devices can be found at http://www.trgpro.com/support/cf_compatible.html. Unfortunately, TRG is the only PalmOS licensee to use this teehnology, and therefore the use of CF cards may be viewed as pseudo-proprietary. The Sony CLIE™, on the other hand, comes with a total of 16 MB of memory: 8 MB on-board RAM with an additional, removable 8 MB via an included Memory Stiek™, whieh fits into the device's Memory Stiek expansion slot.[11] Memory Stiek is a relatively cheap solution to memory expansion, when eompared to Handspring's offerings. Currently, Memory Stiek modules up to 64MB ean be purehased, compared with 16MB expansions made reeently available for Handspring deviees. A GPS receiver and a digital eamera eard may also be used in the Memory Stiek expansion slot;[12] however, like Handspring's Springboard expansion slot, Memory Stiek is proprietary. Given that each eompany uses diffcrent expansion tcchnology, an individual will not be able to interehange modules between different brands of handhelds, a hindrance should one ehoose to upgrade to a different manufacturer's deviee down the road.

One problem that eurrently plagues the PalmOS is that the main on-board memory is treatcd differcntly than that of the Flash ROM, Memory Stick, CF eards, and other memory expansion devices. Should one choose to store editable databases on anything but thc main memory, sueh data may not be aceessible unlcss it is swapped into the main memory whcn needed – a rather tedious proposition. Fortunately, this issue is beginning to be addressed; for instanee, MS Autorun™ permits one to directly launch applications stored on Sony's Memory Stiek.[13] Hopefully this problem will be addressed by Palm in future updates to the OS.

Many handheld models are powered by 2 AAA batteries. The colour Palm IIIe and Sony CLIE have internal rechargeable lithium-ion batteries allowing them to be charged in their docking eradle, whieh is also used to exehange data with a desktop eomputer. All of the high-end models, such as the new Visor Edge and Palm V/Vx™ and m500/505, also offer reehargeable Li-Ion batteries.

High-End Hardware

The Visor Edge and Palm's m500 series modcls are soon expected to dominate the high-end PDA market. The Visor Edge is Handspring's first slim, metal-encased handheld. The Edge will run on PalmOS 3.5.2H with a 33-MHz Motorola Dragonball-VZ processor, and comes with 8 MB of on-board memory. The unit possesses a conneetor that allows for a detachable Springboard slot, or baekpaek to attaeh to the Visor Edge. With this add-on, any of the eurrent Springboard expansion modules may be used. The Edge, quite slim when used alone, can become somewhat bulky with the use of expansion modules.[14] However, the coming months should see thinner deviees produced for the Edge's new, slimmer expansion slot.[15] The Edge is also equipped with a microphone and a LED indieator which acts as a silent, flashing alarm.

Palm is replacing its V-series with the m500 and m505, whieh have monochrome and colour sereens, respectively. The m500 series runs the new PalmOS 4.0, and eomes bundled with software allowing the user to edit Excel spreadsheets and Word doeuments, read eBooks, view video clips and photos, and browse Web eontent off-line. On-line conneetivity is provided via connection to a modem or data-enabled mobile phone. It will use the same

Motorola Dragonball processor as the Visor Edge and Platinum Edge, but it is anticipated that Palm will move to use to use Intel StrongARM processors in 2002 when version 5.0 of the OS debuts. The m500 series has a vibrating alarm and a silent alarm light which doubles as the power button. Probably the most revolutionary part of the m500 series is its dual expandability via the "Universal Connector," which is the connection port for the docking cradle, and the Expansion Card Slot featuring Secure Digital (SD) technology.[17,18]

Secure Digital (SD) technology is the new expansion feature present in the m500 & m505. The SD Card has two major attributes that make it exciting. The first is its size: the SD Card is roughly the size of a postage stamp and the thickness of a credit card, measuring 32 mm long by 24 mm wide by 2.1 mm thick. Thus, products using this technology can expand their memory or add on devices without needing bulky expansion modules.

The second impressive feature of SD Technology, is the third-party support behind this platform. The SD Association is impressive. Matsushita Electric (Panasonic), SanDisk, Toshiba, Compaq, Hewlett Packard, Mitsubishi Electric, NEC, IBM, Sharp, Canon, Nokia, Phillips, Eastman Kodak, Palm and even Microsoft are among the 204 companies currently listed on their website (www.sdcard.org). The SDA describes itself as an open industry standards organization. Established in January 2000, its mission is to set industry standards for the SD Card and promote its wide acceptance in a variety of applications. It claims that the SD Card standard is being built into a wide range of new digital products such as handheld PCs, cellular phones, audio players, automotive multimedia systems, video and digital still cameras. Initially, Palm has made an SD expansion card with 16MB of memory storage available, with larger expansions expected to come in the future.[19,20] One website displays pictures taken from PalmSource 2000, a Palm developers' conference, showing the Panasonic booth displaying SD memory expansion cards up to 1 gigabyte, or 1000 MBs! This site also shows a modem, scanner, MP3 Player, digital camera, and GPS card set to come out for the SD slot.[20] The SD Card is also compatible with existing MultiMedia Cards (MMC), which are now mostly used in cell phones. Transferring data, images and audio files to desktop and notebook computers will be facilitated via a floppy drive SD adapter, parallel port and Universal Serial Bus (USB) port readers, and a PC Card adapter.[21] With such a broad range of corporations supporting the SD technology, one hopes that many companies will be competing for the SD market, thus keeping prices low and supplying consumers with many devices that can use and thus exchange data via these cards.

General and Medical Software

There are several major sites that allow downloads of general PalmOS based software. Among them are Palmgear.com, Tucows.com, and Memoware.com. Palmgear provides "Top 50 Monthly", "Top 50 Downloads" (of all time), "Essentials", and "Gear's Choice" listings. Both Top 50 listings are based on the number of total downloads, while the ranking of the "Essentials" and "Gear's Choice" listings are based on the opinions of the site administrators.[22] Tucows, via their PDA and PalmOS links, presents software sorted into many different categories. "Medical" is a subcategory under the Calculators, Docs and Productivity category headings.[23] Within each subcategory, programs are rated out of 5 "cows". Memoware lists medical software under their Reference category, which has nearly 300 different listings.[24] However, Memoware does not provide software ratings.

A practical way of quickly finding the software you want is to insert the name of the program in the search field at a site such as Palmgear. Most applications can be found this way, including the many free medical programs, among them a pediatric growth chart program, *STAT Growth Charts 1.4*, and a cardiac risk assessment program named *STAT Cardiac Risk 1.1* by StatCoder.[25] A medical calculator that many find very useful is *Mathias Tschopp's MedCalc*.[26] This program assists in computing over 60 different medically-related formulae – a definite must-have for any health-care professional.

AvantGo is a free program that allows web information to be delivered automatically from the web to a handheld whenever a HotSync (a function which synchronizes files between a desktop computer and a handheld) is performed while the user's computer is on-line. For instance, one could set up *AvantGo* to automatically download the most recent edition of the *Canadian Medical Association Journal* (CMAJ).[27] The CMAJ is not alone in taking advantage of this technology to distribute its materials: *AvantGo* is also being used extensively in the business sector. In fact, many web pages can be loaded to your handheld using this technology. As such, *AvantGo* is quickly becoming a standard in the handheld web-media market.

There are also medicine-specific download sites such as healthypalmpilot.com, handheldmed.com and PDAmd.com. Healthypalmpilot currently provides close to 600 resources available for download.[27] A numerical rating, written comments, and the number of total downloads are given for each software item, although generally few people actually rate the software. Handheldmed lists the large reference texts for sale, such as the *Merck Manual*, *Harrison's Principles of Internal Medicine 14e Companion Handbook* and the *5-Minute Clinical Consult*.[29] Lastly, PDAmd provides a limited number of downloads with no ratings, but does allow readers to post discussion items, and provides a variety of PDA-based articles.[30]

ePocrates Inc. provides a free pharmacopoeia (*qRx 4.0*) and an infectious disease guide (*qID 1.0*). *qRx* provides essential information on commonly-prescribed drugs, including adult and pediatric dosing, contraindications, drug-drug interaction information, mechanisms of drug action, and American drug pricing. The AutoUpdate feature provides updates on information such as new U.S. Food and Drug Administration-approved compounds, changes in drug indications and product recall information. Updated information is added to your handheld when it is synchronized with your desktop computer's Internet connection. More than 200,000 health-care professionals, including nearly 100,000 physicians, have used this program since its launch in November 1999.[231]

Medscape.com, via its Medscape Networks and Med Students links,

has a Medscape mobile section, which provides a few free clinical tools for PDAs.[32] Among these are a pharmacopoeia, a medical calculator and an article reader that allows you to view various specialty-related articles on your PDA.

Featured Free Non-Medical Downloads.

Of course, not all software used by medical students and physicians need to revolve solely around medicine. Some other popular, free downloads include *Noah Lite English Dictionary 0.65*, *BigClock 2.82*, and *DiddleBug 2.15*. *Noah Lite* and *BigClock* are fully described and available for download at Palmgear.com. *DiddleBug* is a program that turns the entire PDA screen into a pad which allows you to quickly jot down notes without having to use *Graffiti*, the alphabet writing system that one must normally use under the PalmOS. It also allows you to tag notes with reminder alarms, such that at a specified time, the PDA will beep and the selected note will appear on the screen. All three programs can be consistently found in the "Top 50 Monthly" section of Palmgear.com.

StreetFinder, a map program by Rand McNally & Co., is a very useful program for those new to an area and longtime residents alike.[33] You can choose to install as many maps for as many cities as you want. Each map occupies about 200 KB of memory, while the application program is slightly smaller. If you need to find a specific address, tag a location of interest for quick reference at a later time, or find a restaurant serving pad thai within a given radius from a specified intersection, then this may be the program for you.

Along with the convenience and utility of downloading programs such as these from an online source or sharing files with others comes the risk of exposure to viruses. Six months after the presence of Phage .936, a virus affecting PC–PalmOS interactions, two companies have come forward with full-coverage virus protection. Symantec has released *Norton AntiVirus 2001* for Palm.[34] Its Professional Edition includes a new technology called script blocking; this permits the detection and eradication of script-based viruses and "worms" even before there is a virus definition for the specific virus.[35] *F-Secure Anti-Virus* for PalmOS protects against any known "malware" on the Palm platform, offering on-device protection with automatic updates.[36]

If you have ever considered moving your Adobe Acrobat PDF documents to the PalmOS, there are currently a few options. You can use the free *PDF2DOC* plugin for Adobe Acrobat. This program converts PDF files to a file type that may be viewed by a variety of Doc readers on the Palm.[37] If you wish to preserve PDF formatting and feel comfortable doing a little optimization of the files, Ansyr's *Primer* may be for you. Their 25 KB application program allows you to view modified PDF files on your PalmOS handheld. The file modification uses Primer's Windows-based tools. This solution, however, costs US$50.[38] Adobe has recently released a beta-version of their PalmOS Acrobat Reader, which is freely available for public testing (http://www.adobe.com/products/acrobat/reader for palm.html). What may be of particular use with these PDF file converters, especially for medical students and staff, are various PDF-format medical atlases and other texts.

As noted earlier, there are several sites from which you can download hundreds of freeware or shareware titles. Unfortunately, the authors of such software do not employ standard readers or viewers. Hence, it may be necessary to carry several readers on your handheld, such as *iSilo* for text and web documents,[39] *EZ Reader* for several of the medical textbooks, *HanDBase* for various database files,[40] and *TealDoc*, *TealInfo* and the whole *Teal* software suite which permits viewing of a wide variety of file formats.[41]

Word-Processing and Spreadsheet Capabilities.

Word processing capabilities are available from several third-party software companies. A standard function is the ability to exchange documents with Microsoft (MS) Word, allowing document transferability between handheld and desktop computers. Currently *MegaDoc 1.7*, *Quick Office 5.0* and *Documents To Go Professional 3.004* are the most popular with consumers. All except *MegaDoc* also allow you to also synch spreadsheets with MS Excel; *TinySheet 3.2* allows you to synch with MS Excel only. All are available at Palmgear.com and other major sites. Currently, Palm and Handspring offer fold-out keyboards which make word-processing and spreadsheet capabilities on handhelds more comfortable.

The Future of Handhelds

Why should health-care professionals consider the use of handheld computers? There are several reasons, but those specifically concerning health-care include information management and decision support. If, for example, your patient is currently on several medications, you can use *ePocrates* software to check for known drug-drug interactions or for contraindications to treatment. For students, applications such as the *5-Minute Clinical Consult* provide necessary basic information and treatment guides, while stimulating lateral thinking by providing broad differential diagnoses.

Medical record and patient tracking systems will undoubtedly become more useful as wireless connectivity becomes standard. Health care professionals will be able to access up-to-the-minute information on any of their patients. Other uses will include accessing on-line reference materials, guides, evidence-based medicine tools, and billing systems. The key feature to all of these applications is that they may be accessed at the point-of-care. The fact that Palm, Inc. has announced plans to invest in ePhysician, a company that designs products to help doctors improve patient care and practice efficiencies through handheld services and information delivery, signifies that the role of handhelds in health-care is viewed as a critical market.[42] The future of handhelds may provide medicine-specific expansion devices, standard on-line connectivity and even "eWallet" functionality.

Palm gave some suggestions of future uses that Secure Digital hardware expansions may have in industry-specific fields. In health care, mobile heart monitors, blood pressure monitors and on-the-spot insulin/glucose meters are some of the industry-specific modules that may be developed in the future.[43]

Currently, with the Palm Mobile Internet Kit you can use your Palm handheld in combination with a data-enabled cell phone to

a wireless connection with your Internet Service Provider and download information from the Web onto your Palm handheld screen.[44] This unit works with all Palm-brand models.[45]

It is likely that future models of handhelds, like the current Palm VII, will be wireless-enabled on their own, allowing for such capabilities as instant messaging, e-mailing and web browsing. In fact, Sprint PCS and Palm, Inc. have announced an agreement to market and sell wireless solutions for handhelds (and smartphones) using the PalmOS platform. This will provide Internet content via the Sprint PCS Wireless Web on Palm handhelds or PalmOS smartphones.[46] Currently, Palm.Net which provides wireless capabilities used by the Palm VII is not available in Canada; it is unclear whether Palm, Inc.'s many new alliances will allow for service in this country.

Palm's CEO, Carl Yankowski, performed what he called the world's first commercial credit card purchase using a handheld computer. Using the infrared port on his Palm, Yankowski beamed his personal credit card information to a cashier at a mock Sharper Image store set up on stage at a consumer electronics show. His company plans to turn its handheld computers into "eWallets" that could replace the multitude of cards and paper that most people carry in their wallets, such as their drivers license, library card, health insurance card, credit and debit cards as well as photographs of loved ones.[47]

Undoubtedly, the future of handhelds is bright. The forecast by IDC, a global market intelligence company, predicts worldwide sales for "smart" devices will leap from 12.9 million units in 2000 to over 63.4 million by 2004. Personal companions, a category IDC defines as a step up from personal digital assistants (PDAs), make up the bulk of the smart handheld device market with 73 percent of worldwide shipments in 2000. (Smart handhelds are devices that can be expanded by software downloads or the addition of hardware).[48] With companies like Sega announcing that they will be making video games for PalmOS devices, the demographics of handheld users is also likely to broaden.[49]

Medicine and technology are necessarily intertwined; advances in one can spur progress in the other. As technology progresses, or as medicine demands such progress, the two evolve together. The current popularity of handhelds in the medical field is probably a factor of the high information load of the discipline. Future medicine-specific add-ons such as heart monitors may further expand their functionality in practice.

Currently, we are in the midst of a technological revolution. MP3 technology has gained great popularity, "smart devices" such as smart-phones and handhelds continue to permeate the marketplace, and we may soon see smart-appliances and even smart-automobiles. Perhaps Steve Jobs, Apple's CEO, says it best: we are entering the "digital lifestyle era."[50]

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Canada's "Brain Drain" and Its Impact on Health Care

Vlad Miropolsky, B.Sc. (0T3)

Are We Losing Our Minds?

What is a brain drain? We hear about it very often as the media headlines issue warnings about "brain drain" — the emigration of highly educated and skilled Canadians to the United States. Some eeonomists believe that Canada is suffering from a brain drain. Amongst those eeonomists are Don DeVortez and Samuel Laryea who prepared a study for the C.D. Howe Institute. They claim that the brain drain is real and is eosting eanadian tax payers millions of dollars. On the other side of the debate, there are economists like John Helliwell, who has compared the eurrent trends to the past movements of edueated Canadians to the United States as well as the past and eurrent immigration trends to Canada from abroad. He eoneluded that the movement of edueated Canadians to the United States in the 1990's was relatively small.[1]

Between 1950 and 1963, the number of managers and professionals moving to the United States averaged 2,582 per year, while between 1982-1996 that figure rose to 3,907. However, given population inereases, the proportionate number of skilled people leaving Canada has fallen signifieantly. In 1950-63, about 10% of the available professionals emigrated compared to just 1% in the 1982-96 period. While it eould be argued that the reeent outflow is actually very modest when compared to historical trends, these reported statistics are based on permanent visas issued to Canadians by the United States and do not include the "TN" visas and "L" visas that are both temporary. The emigration of skilled Canadian labour ineludes engineers, eomputer scientists, physieians, nurses, professors, teaehers, managerial personnel and soeial seientists. While the number of "permanent" emigrants to the United States in these professions may have declined, the outlook changes dramatieally if the non-permanent emigrants are ineluded in the analysis, espeeially after the implementation of North Ameriean Free Trade Agreement (NAFTA) in 1993. In 1997, non-permanent emigrants accounted for 94% of the total outflow of skilled Canadians to the United States, as eompared to 77% in 1986. The total number of emigrants, both permanent and non-permanent, jumped from 17,000 in 1989 to 98,000 in 1997. This increase definitely supports the postulated brain drain from Canada.[1] Ineluded in table 1 are the official 1996 migration numbers according to Statisties Canada.

While the evidence indieates that Canada suffers from an overall loss of its skilled workers to the United States, the issue is far more eomplex than it first appears. Losses of highly skilled workers to the United States may have accelerated during the 1990s, but so too did the influx of highly skilled workers into Canada from abroad.[8] During the 1990s, Canada

Table 1
Canadian Immigration and Emigration for Selected Occupations in 1996.

	Immigration to U.S.	Emigration from U.S.	Worldwide Immigration in to Canada	Net Gain or (Drain)
Engineers	506	93	8278	7772
Computer Scientists	148	113	6467	6319
Natural Scientists	195	61	2194	1999
Nurses	1104	28	421	(683)
Physicians	522	7	342	(180)

Source: Statistics Canada

received far more university graduates than it lost. Indeed, the emigrants that emigrated tended to be better-educated than the population as a whole, and were higher-income earners as well as being individuals of prime working age.[4,8]

However, whilst the canadian immigrants may have boasted a higher degree of education, the quality and nature of their education becomes of issue. A 1999 Globe and Mail editorial stated the argument this way: "Trained immigrants coming from the rest of world may not speak English or French well. Moreover, their training may be so different that they may still not meet our standards".[3] As such, it may be problematic to rely on immigrants to fill the gaps left by their canadian emmigrant counterparts, since many lack the North American credentials necessary to practice their profession in Canada.[5] Furthermore, while immigrants with doctorates in chemistry, physics or engineering, or managers with MBAs, can enter Canada with little difficulty and dive into the employment pool as soon as they arrive; physicians and nurses trained in foreign medical schools face the hurdle of Canadian qualifying examinations and the added difficulty of entering into a residency program.[9]

Statistics Canada reports that unlike other professions, the flow of immigrant doctors and nurses into Canada from around the world has been insufficient to supplant those it has lost to the US. Indeed, the number of immigrating physicians and nurses coming to Canada from all over the world combined does not replace those leaving for the US.[3] In the 1990s, the annual loss of both physicians and nurses were equal to more than one-quarter of the annual supply of new graduates. In contrast, the annual loss of engineers, computer scientists and natural scientists was equal to only four per cent of the new supply of graduates in these fields.[3]

The loss of physicians is especially worrisome in light of the young average age of the emigrating physicians leaving behind an aging physician force in Canada. Adding to the loss of physicians is the retirement of about 900 doctors each year.[3]

Why are Canadian doctors and other professionals leaving? What is motivating them to pack up and leave their homeland behind? Simple econometric work indicates that the flow out of Canada is related to the higher tax rate, the difference in professional incomes, the gap in unemployment rates between

Table 2
Physicians Who Moved Abroad and Returned From Abroad, by Province/Territory, Canada, 1995 to 1999[7]

	Moving Abroad					Returning From Abroad				
	1995	1996	1997	1998	1999	1995	1996	1997	1998	1999
Nfld	10	12	10	13	7	4	2	5	2	5
P.E.I.	3	2	1	3	2	2	1	0	0	0
N.S.	58	56	33	25	32	10	9	12	11	17
N.B.	13	12	17	9	1	5	5	2	3	2
Que.	87	108	132	102	102	50	52	52	47	52
Ont.	251	226	235	234	264	80	44	55	121	150
Man.	54	52	36	33	30	27	12	15	14	20
Sask.	54	52	36	33	30	27	12	15	14	20
Alta.	90	118	91	57	49	20	35	33	57	40
B.C.	67	83	72	74	82	45	45	41	43	46
Yukon	0	0	0	0	0	0	0	0	0	0
N.W.T.	1	0	1	1	0	0	0	0	0	0
Canada	674	731	659	569	585	256	218	227	3211	343

Note: Excludes residents. Includes physicians in clinical and/or non-clinical practice
Source: Southam Medical Database, Canadian Institute for Health Information.

the two countries, growth opportunities, greater exposure to leading-edge technology, and a warmer climate. Another factor that makes it easier for Canadians to migrate to the States is the great familiarity with the country and its job opportunities, thus making the States a known territory for the Canadians. Because Canadians tend to outperform similarly trained U.S.-born workers, many U.S. companies aggressively recruit highly educated Canadian. Subjective factors like the quality of life and health care are a lower priority for many of the Canadian emigrants since they are often young and are provided with health coverage by their U.S. employers.[2]

The Number Of Physicians Moving Away

International migration patterns of Canadian physicians have remained relatively constant between 1991 and 1999. Since 1995, the number who moved abroad represented approximately 1% of the available physician supply, while the number who returned from abroad represented between 0.4% and 0.6% of the available supply (Table 2).

The 585 physicians who moved abroad (moving to the United States or another foreign country) in 1999 represented a 3% increase over the 569 who moved abroad in 1998. The 343 physicians who returned from abroad (returning to Canada from the United States or another foreign country) in 1999 represented a 7% increase from the 321 who returned in 1998 (Table 2).

Physicians Moving Abroad – Demographics

Of the 585 physicians who moved away in 1999, the majority were male, specialist physicians and approximately half received their M.D. education within the last 10 years. Over 70% of the physicians who relocated abroad were educated in Canada. The average age of physicians who left in 1999 was 39.7 years, with little difference between the average ages of family physicians (39.4) and specialists (39.8).[7]

Physicians Returning From Abroad – Demographics

The characteristics of the 343 physicians who returned to Canada in 1999 were very similar to those who relocated abroad. Returning physicians were mostly male (71%), specialists (67%) and nearly half had received their medical education within the last 10 years. Approximately 80% of those who returned received their M.D. education in Canada. The average age of physicians who returned from abroad in 1999 was 41.2 years; the average ages of family physicians and specialists who returned from abroad were 40.9 years and 41.4 years, respectively.[7]

The impact of the physician emigration on the health care system is difficult to estimate. From 1995 to 1999, the number of specialists increased by 6.7% in Canada (with some provincial variations) and the number of family physicians remained stable increasing moderately by 0.8% (28,619 to 28,838) (with some provincial variations). However, the small increase in the number of physicians does not compensate for the increase in the Canadian population during the 90s nor for the increasing average age of Canadians, both of which contribute to the increasing demand for physicians.[7]

Contributing Factors to Physician Emigration

One cause that has been cited for the physician drainage has been the federal government's unilateral and repeated decreases in the rate of increase in transfer payments. Beginning in the late '70s with the Established Programs Financing (EPF) and continuing for the next decade and a half, the cuts culminated in April 1996 with severe or successive reductions in the cash transfer payments for health, post-secondary education and social programs.[6] The number of physician emigrants was highest in the mid-1990s, when anger over cuts in provincial health care expenditures was at its peak.[9]

The resulting closure of hospitals, hospital beds and operating rooms, the reduction in medical school admissions and the marked restrictions in the availability of standard diagnostic and therapeutic technologies, including prosthetics and electro-physiological devices have markedly limited physicians in providing needed medical care for their patients. Using magnetic resonance imaging (MRI) units for example: in 1995, Japan led the G-7 countries with 20 MRI units per million population, followed by the U.S. with 15.5 units, while Canada ranked last behind Germany, the UK and France with 1.3 units per million population.[6]

The Canadian research community has also suffered. This sought after world class group of scientists has been faced with shrinking government funding for basic and clinical research. Of the G-7 nations for which the most recent information is available, Canada ranks last in per capita spending for health research.[6] In frustration, and because they are also not able to pursue their research interests, members of the scientific research community are leaving Canada, usually for the U.S., where funds, equipment and staff are made more available to them.

Taxes

Canada has the highest total personal income tax burden among the G-7 countries. When compared to the US, various Canadian tax policies in Canada have resulted in significantly less after tax income.[6] Physicians in Canada feel that the fee-for-service system puts them on a treadmill. They say that "in the U.S. they can work the same hours, but see fewer patients and practice better medicine".[9]

Postgraduate training availability in the U.S. has also contributed to the Canadian physician drainage. In Canada, medical school and residency positions cuts have left little flexibility for graduates trying to enter desirable residencies.

Even medical schools in Canada have played a role by increasing tuition for MD students. The Canadian Association of Interns and Residents (CAIR) and the Canadian Federation of Medical Students (CFMS) estimate that the individual graduating medical student's debt will be up to $140,000 as a result

of these measures. It should, therefore, not come as any surprise that increasing numbers of graduating physicians leave for the U.S. in an attempt to repay their debts more quickly.

An unfortunate cycle of decreasing resources and increasing workloads, coupled with deteriorating working conditions, has pushed a number of physicians and nurses towards the generous employment offers from the U.S. and other countries. The departure of each one of these health care professionals represents the loss of a major public investment in highly educated, skilled and dedicated practitioners and has a direct negative influence on the quality and continuity of care Canadians need.[8]

Conclusion

In July 1999, Prime Minister Jean Chrétien suggested that the hysteria about a brain drain is being inflated by business interests to reinforce their demands for tax cuts. If anyone wanted lower taxes, said the PM, they should move elsewhere.[9]

The current numbers of emigrants are a catastrophic loss for Canada and the more important issue is not how many we are losing, but who we are losing. Unless government takes appropriate action in the near future, there should be grave concern for the future sustainability of our valued health care system.

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History of our hospital

Rizwan Haq, B.Sc. (MD/PhD)

Doing Good:
The Life of Toronto's General Hospital

J.T.H. Connor

University of Toronto Press
2000, 384 pp
$60.00, cloth

The scaffolding is up, the wrecking company has been called in, and the interiors have been stripped of furniture: the Toronto General Hospital is going through another rebirth. The developments are part of Canada's largest health institution's $350 million redevelopment plans, called Project 2003. In the next five years, the scheme calls for the demolition of several buildings, construction of new ones and renovations of others. But just as these plans come to fruition, J.T.H Connor's new book provides an exhaustive account of transformations past. *Doing Good: The Life of Toronto's General Hospital* traces the hospital's transitions from a small shed in the town of York, used as a military hospital in 1812, to a modern, billion-dollar teaching hospital of the University of Toronto. Connor describes not merely the history of the hospital but also the history of an entire culture, "consider[ing] Toronto's general hospital as a social and political barometer." His sweep is vast and impressive.

Connor separates the hospital's history broadly into three parts. Initially, he focuses on the eighteenth and much of the nineteenth century, when the hospital was an institution providing care only for the sick poor. Next, he details its transformation into a public charity, formalized and secularized by governments, and increasingly sustained by state support. Finally, he covers the twentieth century, when the Toronto General Hospital became the dominant academic hospital in Toronto.

Hospital histories are often dry accounts of institutional developments, but Connor's historical context makes this particular description lively and interesting. One peculiar example is the competition between the three Toronto medical schools for medical specimens in the 1840s. As students became more involved in anatomical dissection, the increased demand for cadavers had led to appalling methods of obtaining bodies, including grave robbing. The particularly grizzly discovery of a woman, an apparent anatomical subject, packed in a barrel in the Toronto harbor heightened public suspicions about the motives of medical men, and led to provincial legislation in 1843.

Other instances provide a glimpse of economic pressures. The 1920s, for example, ushered a period of rapid growth: the Toronto General Hospital was over-capacity and had to turn patients away. The hospital responded by building a pavilion for "paying" patients, providing them "all the conveniences of an hotel." This trend of catering to private patients allowed hospitals to become financially solvent in the face of curtailing government support.

Connor meticulously annotates the text with government reports, correspondence, photographs and anecdotal material. But apart from these details, he reconstructs the major trends in hospitals here and abroad: medicalization, intensive technological change and specialization, and the increased role of laboratory research in hospitals. In addressing these points, Connor reminds us that neither as hospitals are sanctuaries from the public, nor is society immune from the influence of hospitals. If the knowledge of the history of Toronto General Hospital informs our understanding of present and future trends, few health professionals will not benefit from reading this book. Undoubtedly, hospitals will continue to be reborn with the changing societal imperatives.

Medicine and the market (1): a marriage made in heaven?

Chris Chong, B.Sc. (OT3)

Code Blue:
Reviving Canada's Health Care System

David Gratzer

ECW Press
1999, 220 pp
$19.95

"The easiest way to re-establish the doctor-patient relationship is through financial ties." Now *that's* faith in market forces. And it's a faith Dr. David Gratzer preaches throughout *Code Blue*, a policy book that takes a searing look at Canada's health care system and offers a right-of-centre solution to medicare's woes.

Gratzer, who wrote this book while attending medical school at the University of Manitoba and is currently a psychiatry resident in Toronto, agrees with the public perception that medicare is faltering. *Code Blue*'s first chapter overflows with newspaper surveys and heartrending anecdotes meant to convince us that our system is collapsing. Subsequent chapters detail why politicians are unwilling to revamp health care (it's too politically sensitive) and why it's a great myth that

Canada's system is better than America's (the statistics are manipulated to appease our anti-American instincts). The final blow Gratzer delivers to Canada's health care system is an argument that its idealistic design ultimately dooms the program in the face of an aging population. The fatal flaw, Gratzer argues, is that "patients bear no direct costs for the medical services they receive." Thus, patients over-consume and send demand soaring. Doctors, who have no real incentive to economize, happily over-provide in the lucrative fee-for service billing environment. The net result? Spiraling costs that make medicare impossible to sustain over the long-term.

But Gratzer believes there's a solution. Drawing on experiments in China, Singapore, and various American companies, he prescribes Medical Savings Accounts (MSAs) as the cure. Essentially, based on their demographics and health needs, people would be given a lump sum of MSA money to shop around for medical services. Go above the limit, and you'll be paying out-of-pocket until you reach a pre-determined deductible, after which government-bought insurance takes over the costs. Go below the limit, and the money left in your MSA is given back to you in some form or other. Under this structure, patients would be encouraged to spend wisely. Competing doctors and health institutions would be compelled to offer patients the most affordable and efficient health care possible. Simply put, allow market forces to solve medicare's crippling supply and demand problems.

Sound good? Gratzer certainly wants the reader to think so. *Code Blue* is not written to be academically objective, but to persuade the general public. The writing is therefore remarkably accessible and clear. At his best, Gratzer seems to be offering fluidly coherent arguments over a friendly cup of joe. However, at times, the attempt to be persistently convincing in a conversational style gives *Code Blue* the same tone as a diet fad book that persuades everyone to eschew carbohydrates. The author's constant presence and lack of overall objectivity leave the reader wary of how much to believe, and hungry for an occasionally less right-wing analysis of medicare.

Indeed, the clear right-wing bias (painfully evident when *Code Blue* calls the old Reform party the only group of "fearless antiestablishmentarians" to have "challenged the *status quo*") is probably the book's greatest weakness. It is certainly not entirely surprising why this book won the conservative Donner Foundation's annual award for best Canadian policy book. While there are biting reviews of why many lefty supporters of the current system are mistaken, that same sharp criticism is not levied towards right-wing claims. Gratzer thus applauds the dismal 25% response rate in a Fraser Institute survey that bolsters his position, but tears apart research that suggests the current medicare format is actually fine. The market is purported to have made basic needs like housing and food readily available, but many would disagree with *Code Blue*'s contention that Canada's housing situation is adequate and that "no one starves." It would be beneficial to have a more objective study of how much market forces can really be relied on to solve medicare's problems. After all, these were the same forces that were supposed to have improved the availability of low cost housing in Toronto, and to have increased California's energy supply; they failed miserably in both cases.

These drawbacks, however, do not negate the many strong elements in *Code Blue*. Canada's medicare desperately needs the book's thorough, critical appraisal. Gratzer's challenge that Canada's health care system is not much better than America's is both courageous and thought provoking. The exposé of our system's fundamental problems, perhaps the book's best chapter, is well constructed and persuasive. Gratzer leaves little doubt that as it exists, medicare has serious flaws that need to be remedied. As such, *Code Blue* is an important read for anyone with an interest in Canada's health care system. But are MSAs and a more right-wing approach the best therapies for our most cherished public program? Let the debate begin.

Medicine and the market (2): a marriage made in hell?

Irfan Dhalla, B.A.Sc. (0T3)

Clear Answers: The Economics and Politics of For-Profit Medicine

Kevin Taft and Gillian Steward

University of Alberta Press
2000, 124 pp
$9.95 (softcover)

Prior to last year, the Alberta legislature had never taken more than 11 hours to decide on the fate a bill. So when Bill 11—the *Alberta Health Protection Act*—was debated for *47 hours*, it was clear that an extraordinary piece of legislation was being passed.

Some critics of the bill, designed to allow for-profit corporations the privilege of performing surgeries requiring overnight hospital stays argued that it would eventually lead to two-tier medicine. Others were not opposed to the bill's principles, but claimed that its implementation would lead to a glut of conflicts of interest. Yet others contended that Bill 11 would, under NAFTA, give foreign companies the right to set up their own operating rooms in Canada. Of course, that's not how the Alberta government viewed the legislation. As

Premier Ralph Klein stated in the legislature, "[Bill 11] enshrines our commitment to the principles of medicare and the Canada Health Act, bans extra billing, prohibits queue-jumping, bans private hospitals, limits contracting out to minor surgeries only, makes it mandatory for contracts to be made public, and leaves medical decisions to physicians."

Sounds good, doesn't it? The public, however, deserves careful analysis — pleasing rhetoric just won't do. Into the controversy stepped two Alberta journalists, quickly preparing and publishing a slim book entitled *Clear Answers: The Economics and Politics of For-Profit Medicine*. The book begins with a thin, seven-page chapter describing the advantages of for-profit health care. Even Karl Marx could have found more good things to say about capitalism as applied to medicine.

Notwithstanding their obvious bias, Kevin Taft and Gillian Steward manage to do a reasonable job presenting the arguments against for-profit medicine in the next few chapters. Citing a dozen or so peer-reviewed studies, the authors mount a persuasive case against American for-profit medicine. The problem, though, is that not all for-profit medicine is American. An analysis of the internal market system used in Britain would have been helpful, and what of the fact that each Canadian doctor is essentially his or her own for-profit enterprise?

Where the book does succeed is in describing the disconcerting links between Alberta's decision makers and those who stand to benefit financially from Bill 11. One company that has lobbied for the passage of Bill 11 somehow managed to recruit the chief operating officer of the Calgary Regional Health Authority (CRHA) to serve as its chief spokesman. As with school boards, it would seem that the public should elect the members of these regional health authorities, but plans for these elections have been delayed repeatedly. According to Taft and Steward, the CRHA awarded its own head of ophthalmology a contract to perform cataract surgery in his private clinic. A few months later, the CRHA hired as its chief medical officer a physician who co-owned a company named Surgical Centres Inc. Taft and Steward point out that when non-elected officials have the power to dole out billions of dollars to private companies, some degree of corruption is almost inevitable.

In the end, the result is mixed: the authors have shed some light, spewed forth a lot of heat, and leave many questions unanswered. *Clear Answers* also suffers from the speed in which it was created. A good editor would have eliminated much repetition and asked the authors to research their weaker chapters more thoroughly. Any book that delves into the murky realms of health economies and promises clear answers is likely to be disappointing. Unfortunately, *Clear Answers* is no exception.

Why poverty is a pathogen

Darrell Tan, B.Sc. (OT2)

Infections and Inequalities: The Modern Plagues

Paul Farmer

University of California Press
1999, 375 pp
$45

"Paul Farmer set out twenty years ago to heal the world. He still thinks he can." So began a recent *New Yorker* article about the author of *Infections and Inequalities*, a book whose central thesis is distilled to this: Social inequality is a pathogen. Farmer has trod this path before; past books such as *AIDS and Accusation*, and *The Uses of Haiti* are powerful, multidisciplinary analyses that inspire the reader to work against the trans-national forces that adversely affect the health status of the global poor.

Child receiving oral polio vaccine on the streets of New Delhi. Courtesy World Health Organization.

Based on 17 years of ethnographic, clinical and research experience, Farmer begins *Infections and Inequalities* by telling the story of HIV/AIDS in the impoverished central plateau of Haiti. He demonstrates how limited life choices in rural Haiti – not hedonistic behaviours – put people at risk for disease. An individual's economic constraints, for instance, often necessitate sexual relationships predicated more on the quest for financial security than on romance. Worse, lack of opportunity forces many young women into the sex tourist trade, an industry that thrives on the economic disparity between the Caribbean islands and their rich northern neighbours. These problems are of course not unique to Haiti, and Farmer uses a similar multidisciplinary approach to analyse the HIV/AIDS pandemic in rich and poor parts of the globe. What Farmer terms the 'structural violence' of racism, sexism and poverty may lead women to forced prostitution in Bombay or unsafe intravenous drug use in inner-city America.

In the last half of the book, Farmer explores how inequality underlies the global resurgence of multi-drug-resistant tuberculosis – whose very label as a 're-emerging infectious disease' betrays a First World bias. Although the increased prevalence of tuberculosis in downtown Toronto is a recent phenomenon, the disease is no newcomer to most of the world's population.

To most readers, the causative links between the social environment and disease are nothing new. What makes Farmer's analysis stand out, however, is his insightful demonstration of how the pathogenicity of inequality has been obscured. For example, he points out that research studies commonly exaggerate the amount of choice people exercise over their own lives. While patient non-compliance is often blamed as the principal factor impeding the success of global tuberculosis control programs, Farmer explains how lack of access to second line drugs and other proxies for inequality are the true reason that programs fail. He similarly points out the danger of anthropological assessments that conflate social inequality with 'cultural difference' in seeking to understand why certain afflictions are much more common in some populations than in others. Finally, Farmer is not afraid to ask challenging questions: why, for example, does current World Health Organization policy deem the treatment of multi-drug resistant tuberculosis in a host of developing countries not 'cost-effective', even though public health authorities routinely pursue aggressive treatment and contact tracing for similar cases in the United States?

Unfortunately, readers who shun dogmatism may be wary of this book. Farmer repeatedly returns to the same arguments about the insidiousness of structural violence and the need for what he calls 'pragmatic solidarity' with the poor, and readers of his other works will recognize this as a familiar refrain. But this apparent weakness – Farmer's obstinacy – may in fact be the book's strength. Farmer's is a rare voice in the medical community, and his insistence that social forces cause disease is both compassionate and convincing. His thesis is simple, yet powerful in providing a unifying analytical approach to global infectious disease problems. His writing gives the reader a useful vocabulary for describing these modern phenomena, and the liberal use of rich ethnographic case studies makes the text highly readable and enjoyable. Armed with this analytical framework and new vocabulary, readers in medicine, medical anthropology and allied disciplines are sure to find *Infections and Inequalities* an instructive and inspiring text.

Darrell Tan is a Canadian representative to the International Federation of Medical Students' Associations, and former co-coordinator of the University of Toronto International Health Program.

Which anatomy books should a medical student choose?

Paolo Mazzotta, B.Sc., M.Sc. (0T4) and Anil J. Misir B.Sc. (0T4)

Grant's Atlas of Anatomy, 10th edition
A. Agur and M. Lee
Lippincott Williams & Wilkins
1999, 760 pp
$82.95 (softcover)

Atlas of Human Anatomy, 2nd edition
F. Netter
Novartis
1998, 525 pp
$98.95 (softcover)

Color Atlas of Anatomy: A Photographic Study of the Human Body, 4th edition
J. Rohen, C. Yakochi and E. Lutjen-Drecoll
Williams & Wilkins
1998, 486 pp
$103.95 (hardcover)

Clinical Anatomy for Medical Students, 6th edition
Richard S. Snell
Lippincott Williams & Wilkins
2000, 898 pp
$83.95 (softcover)

Thompson's Core Textbook of Anatomy, 2nd edition
James S. Thompson
Lippincott Williams & Wilkins
1989, 586 pp
$61.95 (softcover)

Since the time of Leonardo da Vinci, our fascination with the human form has been represented in countless drawings and photographs. For the medical student, the opportunity to learn about the structure of the human body is the first chance to try to understand the complexities and mysteries that it holds. Unlike da Vinci's time, we are in an information age where numerous authors have published a plethora of "expert" and "concise" books describing the anatomy of the human body. This review will examine five popular books (three atlases and two texts) in the hope of helping anatomy students choose the textbook(s) that is right for them.

Of the three atlases, *Grant's* has a number of advantages. First, it was written by two anatomists from the University of Toronto, and therefore is especially attuned to the Canadian medical student's needs. Though it unfortunately has few photographs, the combination of both lifelike and diagrammatic drawings is helpful. Included are relevant radiological pictures as well as surface anatomy. Accompanying text is concise, and limited to summary tables or brief notes giving "just the facts". New for the 10th edition, Agur and Lee have included an excellent cranial nerves section. An additional time saver is the use of coloured tabs to identify regional sections in the book, which is perfect for feverish last minute studying. One final positive feature is the book's aesthetics. Many anatomy drawings in textbooks seem to use a sombre palette; *Grant's* more liberal use of colour is pleasing to the eye and may lead to improved understanding.

Netter also provides a solid atlas of great practicality. Exclusively using colour sketches, Netter provides a bare-bones presentation of the relevant anatomy, excluding photographs and radiological images. As in most geographical atlases, there is little accompanying text. The drawings, however, do provide every possible kind

of view and dissection, from cut-away drawings, to surface anatomy, to functional drawings such as the structure of the kidney tubule. With its straightforward approach, many find this atlas especially useful at the dissecting table.

Rohen and colleagues' atlas differs from the previous two in that it consists almost entirely of labelled photographs of dissected cadavers. While there are occasional explanatory diagrams, the main attraction is the 947 colour photographs and radiological images. Accompanying text is limited mainly to captions. Of great help is the use of injected coloured latex for blood and lymphatic vessels. As a photographic atlas, Rohen provides a good proxy for the dissection table. While this is not an excuse to avoid visiting the lab, Rohen offers a good way to learn structures in more realistic way than using drawings alone.

Although most students of anatomy associate the study of the human body with pictures or photos, a textbook is an important and useful adjunct to any atlas. Both Snell's *Clinical Anatomy for Medical Students* and *Thompson's Core Textbook of Anatomy* are up to the task of charting a path for the inexperienced student through a voyage of discovery. As with the reviewed atlases, both texts organize the body into regions. Both texts are also clear and concise with a level of detail that does not overwhelm the amateur. Important terminology is in bold print, helpful in scanning the text for areas of interest. However, beyond organization and case of reading, the two texts have distinct features.

Snell's *Clinical Anatomy of Medical Students* organizes each chapter into four sections: Basic Anatomy, Radiographic Anatomy, Surface Anatomy and Clinical Notes. Snell also includes an excellent appendix of tables summarizing the major muscles by region, including movements, insertions and nerve innervations. As one reads along, the ideas from the Basic Anatomy section are reinforced with each successive section. Depending on one's learning style, this may be an advantage or disadvantage. Breaking up the chapter material in this way can break the flow of reading, forcing the reader to flip back and forth between sections.

Radiology and surface anatomy are of prime importance and Snell manages to include excellent photographs and x-rays, CT scans and MRIs for each chapter, with diagrammatic representations to assist in interpretation. Snell also includes a large number of drawings in colour and black-and-white to help accentuate the text. The colour drawings are used wisely, primarily to highlight structures of interest. A unique feature of Snell's text is the inclusion at the end of each chapter of Clinical Solving Problems with explanations as well as USMLE Sample Questions with answers. These may be useful for future reference or for immediate reinforcement of newly acquired knowledge.

Thompson's Core Textbook of Anatomy chooses a different route. By merging diagrams, tables and clinical concepts within the body of each chapter, the author allows for a fluid flow of ideas and concepts that keeps the reader focused on one region at a time. Unlike Snell, Thompson uses black-and-white drawings with occasional monochrome colour. However, the drawings are simpler and clearer than those in Snell's text and complement well the accompanying text. The important terminology is in bold print and the clinical concepts are italicized, which assists in easy location. Although Thompson includes only limited surface anatomy and no radiological images, the absence of these components does not affect his book's strengths, since an accompanying atlas, such as Grant's, can substitute well in these areas.

It is clear that the different anatomy texts and atlases have individual strengths and weaknesses. A student's choice of reference will be based on his or her own learning style and previous experience. Cost, which may be a deciding factor, varies substantially between books. As well, previous incarnations are often available at a local library or book sale. Keep in mind that human evolution proceeds slowly: anatomy has not changed much even since da Vinci's time!

Using references in combination may be the introductory student's best bet. Moreover, using text references should not preclude the use of computer programs or other learning aids. But even computer-based tools can't quite replace time spent in class or the anatomy lab. Like the Renaissance man da Vinci, a variety of sources must be used to fully appreciate the mysteries of the human body.

Paul Mazzotta and Anil Misir collectively used all the reviewed textbooks during their first year of medical school.

Buffing and turfing gomers in God's house

Andrea Waddell, B.Sc. (OT3)

The House of God

Samuel Shem;
introduction by John Updike

Dell Distributing
2000 (first published in 1978)
429 pp

And the delivery of medical care? Farce. BUFF n' TURF. Revolving door. I wasn't sitting at the end of the ambulance ride, no. There was no glamour in this.

– Samuel Shem's
The House of God

Every medical student, resident and physician can remember the first time they read *The House of God* by Samuel Shem. First published in 1978, *The House of God* follows six interns through their one-year rotating internship. From the title, one might be fooled into thinking this would be a pious story of altruism and self-realisation as these young doctors face the trials of internship. Alas, the title is ironic; what little altruism these six interns possess on page one is quickly dissipated by their initiation into the world of the *gomers* and the dying young.

For those who have not yet read the book, a gomer (Get Out of My Emergency Room) is an impossibly old, unbelievably ill individual who is impervious to death. We have all met gomers; they are the patients who have current medication lists two pages long including drugs that *ePocrates* predicts will cause instant death if used together. Their previous medical histories read like a convoluted PBL case and are rife with horrendous complications. According to all the textbooks, they should be dead, yet here they are before you — a feat of nature, a triumph of modern medicine.

It is these gomers that bring about the gradual breakdown of each of the interns. The gomers' continued life in the face of disease and suffering brings the interns face to face with the powerlessness of medicine. Medicine, it seems, is not an all-knowing, all-healing profession; no, it seems that "the main source of illness in this world is the doctor's own illness: his compulsion to cure and his fraudulent belief that he can." (What? They didn't teach us *that* in medical school.)

THE LAWS OF THE HOUSE OF GOD

I. Gomers don't die.
II. Gomers go to ground.
III. At a cardiac arrest, the first procedure is to take your own pulse.
IV. The patient is the one with the disease.
V. Placement comes first.
VI. There is no body cavity that cannot be reached with a #14 needle and a good strong arm.
VII. Age + BUN = Lasix dose.
VIII. They can always hurt you more.
IX. The only good admission is a dead admission.
X. If you don't take a temperature, you can't find a fever.
XI. Show me a BMS who only triples my work and I will kiss his feet.
XII. If the radiology resident and the BMS both see a lesion on the chest x-ray, there can be no lesion
XIII. The delivery of medical care is to do as much nothing as possible.

The realisation that we mostly offer comfort, not cures, comes to each of us slowly. It is easy to get caught up in the fervour of the heroic act and to forget to pause and ask if the patient's desires are being considered. There is a natural curiosity that drives us to push the limits of medicine to see if this time we can save someone. *The House of God* is a frank examination of the methods one uses to cope in an environment of suffering and death.

The book is also very, very funny, and I often found myself guiltily laughing at Shem's vivid patient descriptions. These depictions, however, made me wonder if *The House of God* shouldn't be under restricted access; I hated to think of a patient reading it. But then I realized that the reason I feared my patients reading the book was that it would remove my capacity to hide behind the white-coated illusion of unfaltering courage and knowledge. To me, that is what this book is about – confronting the humanity of medicine along with the science.

As you read *The House of God*, it becomes clear that only a doctor could have been its author. Samuel Shem is actually a pen name for Stephen J. Bergman, a lecturer in psychiatry at Harvard University. Although he has continued to maintain that this book is a work of fiction, it is apparent that the message he tried to convey with *The House of God* remains important to him. More than 20 years after its initial publication, Shem continues to give lectures on "How to Stay Human in Medicine" using examples from *The House of God* and it's sequel *Mount Misery*.

The House of God is a must-read for medical students, especially as clerkship approaches and we need to prepare for gomers of our own. Although a classic and a million-copy bestseller, the book is certainly not without faults. *The House of God* is a reflection of the era in which it was written – the late 1970s. Women are poorly represented: there is only one female resident, and she has limited humanity. The book also serves to perpetuate the myth of the willing and nubile nurse; clearly Samuel Shem's wild imagination has resulted in some sordid and unrealistic encounters.

It is tempting to believe that the elimination of the rotating internship has led to the elimination of the accompanying bitter disillusionment – don't fall into that trap. Like most things in our medical curriculum it has simply been pushed earlier. So, in your lab coat pocket along with your Palm Pilot, keep your tattered copy of this book for quick reference to the laws of the House of God. They just might keep you sane.

Norvasc* (amlodipine besylate)

Brief Prescribing Information
NORVASC*
(amlodipine besylate)
Tablets 2.5, 5 and 10 mg
Antihypertensive-Antianginal Agent

ACTION AND CLINICAL PHARMACOLOGY

NORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

INDICATIONS AND CLINICAL USE

Hypertension

NORVASC (amlodipine besylate) is indicated in the treatment of mild-to-moderate essential hypertension.

NORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. **NORVASC** can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of **NORVASC** with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.

Chronic Stable Angina

NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. **NORVASC** may be tried in combination with beta-blockers in chronic stable angina, in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS

NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

WARNINGS

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Outflow Obstruction (Aortic Stenosis)

NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients with Impaired Hepatic Function

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. **NORVASC** should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).

Beta-blocker Withdrawal

NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

PRECAUTIONS

Use in Patients with Congestive Heart Failure

Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that **NORVASC** had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.

Hypotension

NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.

Peripheral Edema

Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Use in Pregnancy

Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with **NORVASC** in pregnant women. **NORVASC** should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, **NORVASC** should not be given to nursing mothers.

Use in Children

The use of **NORVASC** is not recommended in children since safety and efficacy have not been established in that population.

Use in Elderly

In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. **NORVASC** should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).

Interaction with Grapefruit Juice

Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice.

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Co-administration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.

Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.

Cimetidine, Warfarin, Cyclosporin, Digoxin: Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:

- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin**.
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

Antacids

Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.

Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with **NORVASC**, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

Sildenafil: A single 100 mg dose of sildenafil (VIAGRA) in subjects with essential hypertension had no effect on AUC_t or C_{max} of amlodipine. When sildenafil (100 mg) was co-administered with amlodipine, 5 or 10 mg in hypertensive patients, the mean additional reduction of supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.

Special Studies: Effect of **NORVASC** on other agents.

Atorvastatin: In healthy volunteers, co-administration of multiple 10 mg doses of **NORVASC** with 80 mg of atorvastatin resulted in no significant change in the AUC_t, C_{max} or T_{max} of atorvastatin.

ADVERSE REACTIONS

NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity

Hypertension

In the 805 hypertensive patients treated with **NORVASC** in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):

Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).

Angina

In the controlled clinical trials in 909 angina patients treated with **NORVASC**, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%). The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):

Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** vision abnormal (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).

NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina

The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, peripheral neuropathy, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapular, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leucopenia, purpura, thrombocytopenia.

†These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of **NORVASC** (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment

Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As **NORVASC** is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION

Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of **NORVASC** (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily

Use in the Elderly or in Patients with Impaired Renal Function

The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).

Use in Patients with Impaired Hepatic Function

Dosage requirements have not been established in patients with impaired hepatic function. When **NORVASC** is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS

Availability

NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE

Store at 15-30°C. Protect from light.

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UTMJ

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INSTRUCTIONS TO AUTHORS 2000-2001

The University of Toronto Medical Journal (*UTMJ*), an official journal of the University of Toronto Faculty of Medicine, is devoted to the publication of significant, original studies and review articles in all areas of basic, clinical, translational and epidemiological medical research, as well as medical education, medical ethics, medical jurisprudence, and the history of medicine. Submissions of editorials, letters, and comments regarding matters pertinent to the areas above are also welcomed. In addition, submission of case reports in any format will be entertained. All submissions must be in the English language.

Procedure for Submission

Contributions should be addressed to: The Editors, *UTMJ*, Medical Sciences Building, Room 2141, 1 King's College Circle, University of Toronto, Toronto, Ontario, M5S 1A8, Canada; Phone: (416) 946-3047. e-mail: editors.utmj@utoronto.ca website: www.utmj.org

The deadlines for submissions for the 78th edition of the *UTMJ* are: September 22, 2000; January 8, 2001; and March 16, 2001.

The paper should be submitted by an author, preferably the principal author, who should indicate in a covering letter:

1. that the paper is being submitted for consideration for publication in *UTMJ*;

2. the exact address to which all related correspondence should be sent and the email, telephone, and FAX numbers at which the author can be reached;

3. that neither the submitted manuscript nor any similar paper, other than an abstract of preliminary communication, has been or will be submitted to, or published, in any other primary scientific journal;

4. that all of the authors are aware of, and agree to, the content of the manuscript and that authorization has been given to use any information conveyed by either personal communication or release of unpublished experimental data;

5. three to six key words describing the paper, to assist in the selection of the reviewers.

Original Submissions must include:

1. The author's covering letter containing the above information.

2. Four copies of the manuscript and four sets of original illustrations. Illustrations should be Camera-Ready black and white photographs, figures, line drawings, and graphs.

3. Computer diskette containing all the parts of the manuscript on ONE file. Refer to the following Editing Process section for more details.

Organization

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Title Page

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3. Smith MHD and Teele DW. (1995). Tubercuiosis. *In: Infectious diseases of the fetus and newborn infant, 4th ed.* Remington JS and Klein JO (eds). WB Saunders: Philadelphia, pp. 1074-1086.

4. Podolsky DK and KJ Isselbacher. (1998). Major complications of cirrhosis (ascites). *In: Harrison's Principals of Internal Medicine, 14th ed.* Fauci AS et al. (eds). McGraw-Hill, New York, pp. 210-214.

Books, theses, or comparable publication

5. Pressaeo J and Yu H. (1996). *Pharmacological Treatment of Diseases.* Urban Angel Medical Books Inc: Toronto.

NEW: Web documents

6. Jacobson, J. W., Muliek, J. A., & Schwartz, A. A. (1995). A history of facilitated communication: Science, pseudoscience, and antiscience: Science working group on facilitated communication. American Psychologist, 50, 750–765. Retrieved January 25, 1996, from the World Wide Web: http://www.apa.org/journals/jacobson.html

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